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Note

Synthesis and evaluation of some new substituted phenylthiazole derivatives and their antitubercular activity

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A new series of substituted phenylthiazole derivatives have been synthesized and the structures of these compounds have been established on the basis of spectral and elemental analysis. All compounds have been screened for antitubercular activity by Middle brook 7H9 agar medium against $H_{37}Rv$. strain. Most of these compounds have shown promising antitubercular activity.

Keywords: Phenylthiazole, antitubercular, Middle brook 7H9

The advent of drug discovery techniques such as combinatorial chemistry and high-throughput screening (HTS), rapid identification of numerous hits has now become a reality[1,2]. Medicinal chemists have immeasurable quest for innovation, blending synthetic chemistry, molecular modeling, computational biology, structural genomic, drug repositioning and pharmacology to discovery and design new drugs and investigate their interaction on the substrate models and at the cellular level.

Several physiological activities of various thiazole derivatives, have proved the efficacy in combating various diseases and found to have good antitubercular activity[3] and it has been observed that thiazole analogues incorporated with different nuclei have shown various pharmacological profile[4,5].

Results and Discussion

All the compounds were screened for anti-tubercular activity by Middle brook 7H9 agar medium method against $H_{37}Rv$ strain. However, the compounds **6, 9, 11, 13, 14, 15, 17, 18, 21, 23, 25, 30, 31** and **32** have shown promising antitubercular activity, while the remaining compounds have shown moderate antitubercular activity, when compared with the standard drug Streptomycin.

Materials and Methods

Antitubercular Activity[6,7]

The antitubercular screening was carried out by Middle brook 7H9 agar medium against $H_{37}Rv$. Strain. The media containing different derivatives **(6** to **25** and **30** to **33)**, standard drug and control was inoculated with mycobacterium tuberculosis of $H_{37}Rv$ Strain. The inoculated bottles were incubated for 37°C for 4 weeks. At the end of 4 weeks they were checked for growth. The MIC of the standard drug streptomycin is 10 mcg/mL.

Experimental Section

All melting points were determined in open capillary method and are uncorrected. IR spectra were recorded on Thermo Nicolet IR 200 spectro-photometer using KBr disc method. The ^1H NMR Spectra were recorded on sophisticated multinuclear FT-NMR Spectrometer model Avance-II (Bruker) using DMSO-d_6 as solvent and tetramethylsilane as internal standard. Perkin Elmer 2400 CHN Elemental Analyzer was used to determine the percentages of C, H and N.

Procedure for synthesis of 4-(4,5-diphenylthiazol-2-yl) derivative, 1 (Ref 8,9)

A mixture of 25 mmole (5.25 g) benzil, 25 mmole of substituted aldehyde and 10 g of ammonium thiocynate were taken in a 250 mL round bottomed flask attached to a reflux condenser and refluxed with 5 mL of glacial acetic acid for 4 hr. The resultant mixture was left overnight and filtered to remove any precipitate. Then 250 mL distilled water was added to the filtrate and precipitate formed was collected. The filterate was neutralized with ammonium hydroxide and the second crop of the solid was collected. Both solid crops were combined and recrystallized from ethanol. Yield 83% and m.p. 162-64°C.

Similarly, the other reactions were carried out under the same condition. **1a**: Yield 78%,

m.p.140-42°C; **1b**: 80%, m.p. 165-67°C; **1c**: 77%, m.p. 156-58°C respectively.

Procedure for synthesis of 2-(4-(4,5-diphenylthiazol-2-yl) phenoxy) acetyl chloride, 2 (Ref 8,9)

An exact quantity of 0.01 mole (3.48 g) of 4-(4,5-diphenylthiazol-2-yl) **1** was dissolved in 25 mL of glacial acetic acid and 25 mL of saturated solution of sodium acetate with gentle warming. The solution was cooled in ice bath with stirring. To this solution was added drop wise a solution of chloroacetyl chloride (0.12 mole) at 0°C. After 30 min white product was separated by filtration. The product was washed with 50% aqueous acetic acid and finally with water. It was recrystallized from ethanol. Yield 71% and m.p. 226-28°C. Similarly, **3**, **4** and **5** were synthesized under same condition. **3**: Yield 68% and m.p. 234-36°C; **4**: 70% and m.p. 222-24°C; **5**: 74% m.p. 220-22°C.

Procedure for synthesis of 4-(2-(4-(4,5-diphenylthiazol-2-yl)phenoxy)acetamido)-2-hydroxybenzoic acid, 6 (Ref 10)

A mixture of 0.01 mole (4.5 g) of 2-(4-(4,5-diphenylthiazol-2-yl)phenoxy) acetyl chloride **2** and 0.01 mole of substituted amino compounds were taken in a 100 mL round bottom flask. To this 2.5 mL of 1,4 –dioxane and 0.01 g or 0.01 mL of triethylamine (TEA) solution was added and the flask was placed in the microwave at 60% power for 4 min. It was then cooled and poured on crushed ice. The product was filtered, washed with 1% potassium bicarbonate and water, the resultant solid mass was dried and it was recrystallized from ethanol. Yield 78% and m.p. 231-33°C. Similarly, compounds **7** to **25** were synthesized under same condition. Yield and m.p are mentioned in **Table I**.

Procedure for synthesis of 2-(4-(4-((2*E*,4*Z*)-hepta-2,4,6-trien-3-yl)-5-phenylthiazol-2-yl)phenoxy)acetohydrazide, 26 (Ref 11)

A mixture of 0.01 mole (4.05 g) 2-(4-(4,5-diphenylthiazol-2-yl)phenoxy) acetyl chloride **2** and 10 mL of hydrazine hydrate were taken in 250 mL round bottomed flask and refluxed for 2 hr. The clear reaction mixture was kept overnight. The solid mass thus separated out was filtered and dried. The same was recrystallized from ethanol. Yield: 62%, m.p. 236-38°C. Similarly, **27**, **28** and **29** were synthesized under same condition. **27**: Yield 65%, m.p. 240-42°C; **28**: Yield 60%, m.p. 238-40°C; **29**: Yield 64%, m.p. 235-37°C.

Procedure for synthesis of 1-(2(4-(4-((2*E*,4*Z*)-hepta-2,4,6-trien-3-yl)-5-phenylthiazol-2-yl)phenoxy)acetyl)-3-methyl-1*H*-pyrazol-5(4*H*-one), 30 (Ref 12)

A mixture of 0.01 mole (4.17 g) of 2-(4-(4-((2*E*,4*Z*)-hepta-2,4,6-trien-3-yl)-5-phenylthiazol-2-yl)-phenoxy)acetohydrazide **26** and 0.01 mole (13 mL) of ethylacetoacetate were taken in round bottom flask and refluxed for 4 hr. The resultant brownish clear solution formed was left overnight. The white solid was separated by filtration and dried. The same was recrystallized from ethanol. Yield 54%, m.p. 275-77°C. The compounds **31, 32** and **33** were synthesized following a similar procedure. Yield and m.p. are mentioned in **Table I**.

Spectral characterization data

6: ^{1}H NMR (DMSO-d_6): δ 9.71 (1H of NH), 7.3-7.9 (10 H m Ar CH), 7.05-7.2 (3 H Ar of PAS), 3.64 (2 H of CH_2).

7: ^{1}H NMR (DMSO-d_6): δ 9.6-9.7 (2H d NH of INH), 7.0-7.9 (14 H m Ar CH), 6.83-6.86 (4 H of INH), 3.8 (4H of CH_2).

9: ^{1}H NMR (DMSO-d_6): δ 9.8 (1H of tetrazole), 9.3 (1H of NH), 7.05-7.79 (14H m Ar CH), 3.62 (2 H of CH_2).

11: ^{1}H NMR (DMSO-d_6): δ 9.64 (1H of NH), 7.2-7.3 (10 H m Ar CH), 7.55-7.57 (3 H Ar of PAS), 3.3 (2 H of CH_2).

13: ^{1}H NMR (DMSO-d_6): δ 9.6-9.8 (2H d of Sulphanilamide), 9.3 (1H of NH), 7.1-7.9 (10 H m Ar CH), 7.0-7.4 (4H of thiazole), 2.5 (4 H of CH_2).

15: MS: *m/z* 463 ($M^{+\bullet}$). Calcd Mol. Wt. 462.

16: ^{1}H NMR (DMSO-d_6): δ 9.85 (1H of NH), 7.1 -8.05 (14 H m Ar CH), 7.53-7.9 (3 H Ar of PAS), 3.84 (2 H of CH_2).

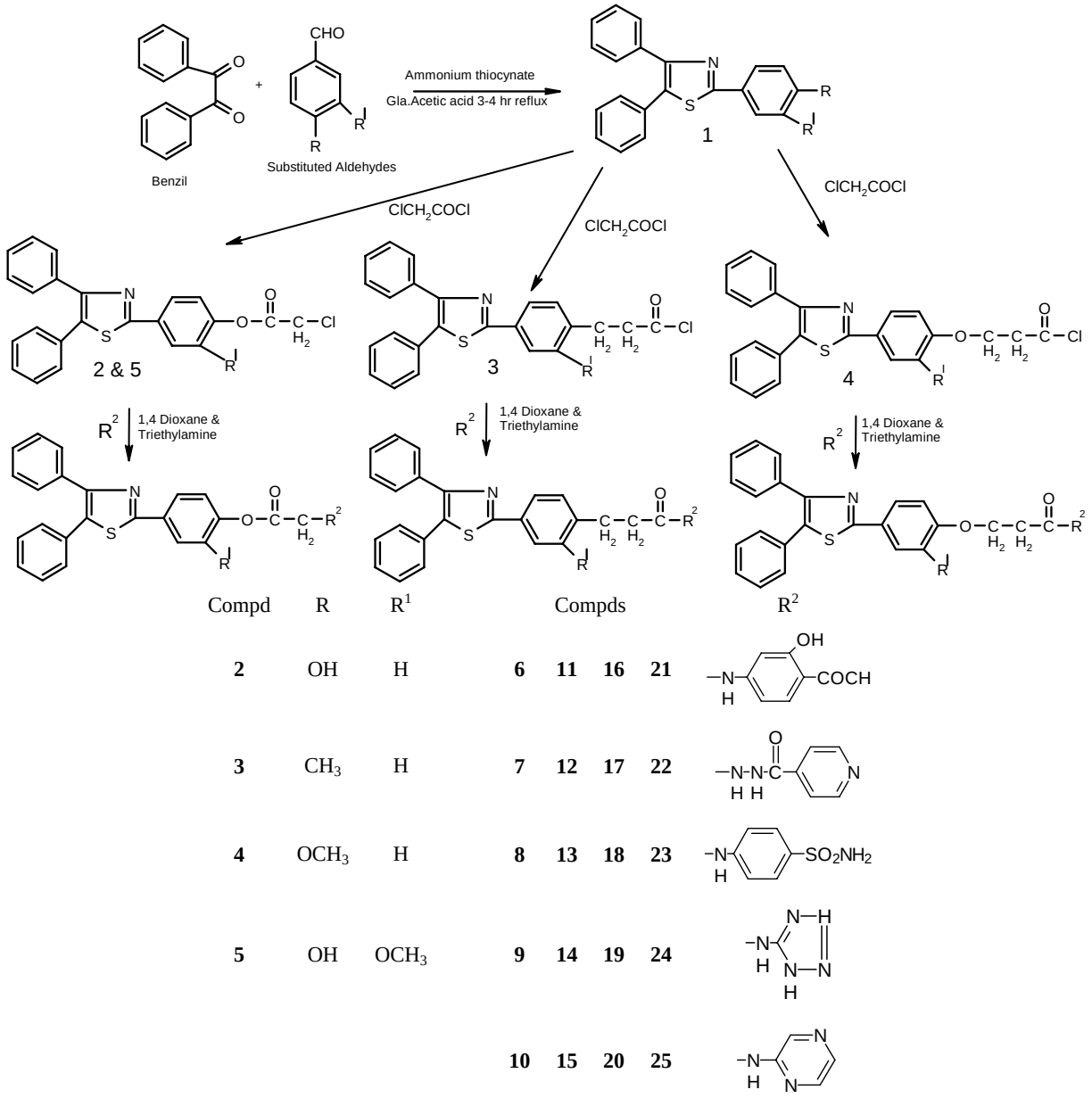
17: ^{1}H NMR (DMSO-d_6): δ 9.4-9.9 (2H d NH of INH), 7.18-8.05 (14 H m Ar CH), 6.9-7.07 (4 H of INH), 3.8 (4H of CH_2).

18: ^{1}H NMR (DMSO-d_6): δ 8.07 (2H d of Sulphanilamide), 7.35 (1H of NH), 7.05-7.84 (14 H m Ar CH), 7.01-6.06 (4H of Sulphanilamide), 3.8 (4 H of CH_2).

19: ^{1}H NMR (DMSO-d_6): δ 9.8 (1H of tetrazole), 9.6 (1H of NH), 7.03-7.94 (14H m Ar CH), 3.8 (2 H of CH_2).

Table I — Analytical and physicochemical data of the synthesized compounds

Compd	Mol. formula	Mol. Wt.	m.p. °C	Yield %	Elemental analyses Found % (Calcd)		
					C	H	N
6	$C_{30}H_{22}N_2O_5S$	522	231-33	78	69.12 (69.04	4.24 4.22	5.36 5.29)
7	$C_{29}H_{23}N_3O_4S_2$	541	189-92	81	64.3 (63.7	4.28 4.22	7.76 7.71)
8	$C_{28}H_{23}N_3O_4S_2$	529	212-14	66	63.5 (63.0	4.38 4.21	7.93 7.89)
9	$C_{24}H_{18}N_6O_2S$	454	254-56	75	63.4 (63.6	3.99 3.80	18.4 18.2)
10	$C_{27}H_{20}N_4O_2S$	464	264-65	84	69.8 (69.0	4.34 4.27	12.0 12.4)
11	$C_{31}H_{24}N_2O_4S$	520	286-88	71	71.5 (70.8	4.65 4.61	5.5 5.55)
12	$C_{30}H_{24}N_4O_2S$	504	213-16	67	71.4 (71.1	4.79 4.70	11.1 10.9)
13	$C_{30}H_{25}N_3O_3S$	539	294-96	80	66.7 (65.8	4.67 4.60	7.59 7.64)
14	$C_{25}H_{21}N_6OS$	453	297-99	83	66.2 (66.4	4.67 4.59	18.5 18.9)
15	$C_{28}H_{22}N_4OS$	462	288-90	75	72.7 (72.0	4.79 4.72	12.1 12.9)
16	$C_{31}H_{24}N_2O_5S$	536	293-95	73	69.3 (69.0	4.51 4.50	5.22 5.18)
17	$C_{30}H_{24}N_4O_3S$	520	277-79	68	69.2 (70.0	4.65 4.52	10.7 10.2)
18	$C_{30}H_{22}N_2O_5S$	555	244-46	72	64.8 (65.1	4.53 4.46	7.56 7.49)
19	$C_{30}H_{25}N_3O_4S_2$	469	291-93	86	63.9 (62.7	4.51 4.44	17.9 17.1)
20	$C_{28}H_{22}N_4O_2S$	478	208-10	74	70.2 (69.04	4.6 4.3	11.7 11.0)
21	$C_{31}H_{24}N_2O_6S$	552	251-54	65	67.2 (69.04	4.38 4.26	5.07 5.03)
22	$C_{30}H_{24}N_4O_4S$	485	227-29	73	61.3 (69.04	4.36 4.35	17.3 17.1)
23	$C_{30}H_{25}N_3O_5S_2$	571	293-95	69	63.0 (69.04	4.41 4.32	7.35 7.39)
24	$C_{25}H_{21}N_6O_3S$	536	285-87	80	67.1 (69.04	4.51 4.59	10.4 11.0)
25	$C_{28}H_{22}N_4O_3S$	494	233-35	67	68.0 (69.04	4.48 4.49	11.3 11.1)
30	$C_{28}H_{23}N_3O_4S$	497	291-93	73	67.5 (69.04	4.66 4.61	8.44 8.39)
31	$C_{29}H_{27}N_3O_2S$	481	212-24	59	72.3 (69.04	5.65 5.57	8.71 7.80)
32	$C_{29}H_{27}N_3O_3S$	497	246-48	78	70.0 (69.04	5.46 5.36	8.43 8.39)
33	$C_{29}H_{27}N_3O_4S$	513	249-51	64	67.0 (69.04	5.31 5.23	8.12 8.19)



Compd	R	R^1	Compds				R^2
2	OH	H	**6**	**11**	**16**	**21**	
3	CH_3	H	**7**	**12**	**17**	**22**	
4	OCH_3	H	**8**	**13**	**18**	**23**	
5	OH	OCH_3	**9**	**14**	**19**	**24**	
			10	**15**	**20**	**25**	

Scheme I

22: ^{1}H NMR (DMSO-d_6): δ 9.3-9.67 (2H d NH of INH), 6.9-7.8 (14 H m Ar CH), 3.9 (2 H of CH_2), 3.1 (3 H of CH_3).

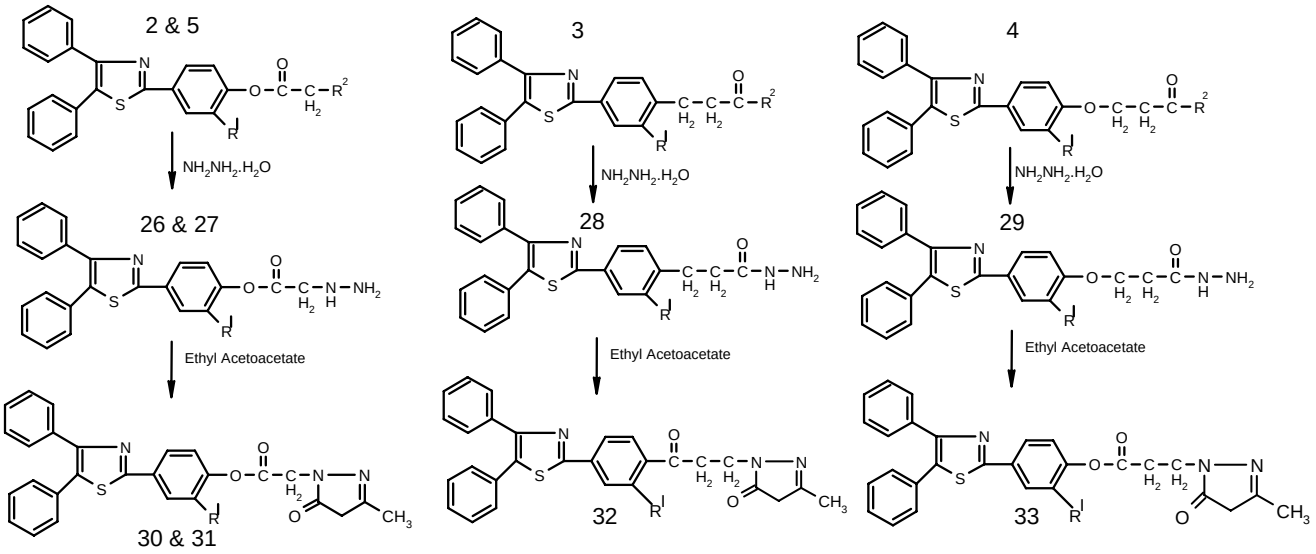
24: MS: *m/z* 485 ($M^{+\bullet}$). Calcd Mol. Wt. 485.

30: ^{1}H NMR (DMSO-d_6): δ 6.9-8.06 (14 H m Ar CH), 6.1 2 (H s CH_2), 3.8 (3 H of CH_3), 2.57 (2 H of pyrazolone).

32: ^{1}H NMR (DMSO-d_6): δ 7.2-8.0 (14 H m Ar CH), 2.58 (3 H of CH_3), 2.31-2.37 (4 H of CH_2), 2.57 (2 H of pyrazolone); MS: *m/z* 484 ($M^{+\bullet}$). Calcd Mol. Wt. 481.

Conclusion

The title compounds were synthesized as per the **Scheme I** and **Scheme II**. The structures of the compounds were confirmed by IR, NMR, and elemental analysis. All these compounds were screened for antitubercular activity by Middle Brook 7H9 method using H_{37}Rv strain. Most of the compounds have shown promising antitubercular activity. Compounds **6, 9, 11, 14, 15, 18, 21, 23, 30** and **32** have shown maximum activity. However, standard antiubercular drug streptomycin is found to have MIC at 10 mcg/ mL. Results are mentioned in **Table II**.



Scheme II

Table II — Antitubercular activity of the synthesized compounds

S. No.	Compd	50 mcg/mL	100 mcg/mL	S. No.	Compd	50 mcg/mL	100 mcg/mL
6	**A_1**	S	S	18	**C_3**	S	S
7	**A_2**	R	R	19	**C_4**	R	R
8	**A_3**	R	R	20	**C_5**	R	R
9	**A_4**	S	S	21	**D_1**	S	S
10	**A_5**	R	R	22	**D_2**	R	R
11	**B_1**	S	S	23	**D_3**	S	S
12	**B_2**	R	R	24	**D_4**	R	R
13	**B_3**	R	S	25	**D_5**	R	S
14	**B_4**	S	S	30	**E_1**	S	S
15	**B_5**	S	S	31	**E_2**	S	S
16	**C_1**	R	R	32	**E_3**	R	R
17	**C2**	R	S	33	**E_4**	R	S
					Streptomycin	S	S

R denotes Resistant and S denotes Sensitive.

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