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Synthesis and selective antitubercular and antimicrobial inhibitory activity of 1-acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives

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Abstract: The new compounds 1-aryl-3-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-2-propen-1-ones **2a–l** were prepared by the condensation of 1-phenyl-3-[*p*-(methylthio)phenyl]-4-formylpyrazole **1** with different aryl ketones. Compounds **2a–l** in reaction with hydrazine hydrate yielded 3-aryl-5-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-4,5-dihydro-(1*H*)-pyrazoles **3a–l** and in the presence of hydrazine hydrate in glacial acetic acid gave 1-acetyl-3-aryl-5-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-4,5-dihydro-(1*H*)-pyrazoles **4a–l**. These compounds were tested *in vitro* for their antitubercular and antimicrobial activities. The *in vitro* antimycobacterial activity of the newly synthesized compounds was investigated against *Mycobacterium tuberculosis* H_{37}RV (ATCC 27294) in BACTEC 12B medium using the ALAMAR radiometric system. The antimicrobial *in vitro* activity was tested against *Bacillus coccous*, *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris* and antifungal activity against *Aspergillus niger*. The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data.

Keywords: pyrazole, pyrazolyl pyrazolines, antitubercular activity, antimicrobial activity.

INTRODUCTION

The synthesis of pyrazoles remains of great interest due to the wide applications of such heterocycles in the pharmaceutical and agrochemical industry. Pyrazole derivatives were reported to possess significant antibacterial,[1] p-38α MAP kinase inhibitory,[2] monoamine oxidase inhibitory activities,[3] insecticidal,[4] anticancer,[5] anti-HIV,[6] herbicidal,[7] *etc*. This gave a great impetus to the search for potential pharmacologically active drugs carrying pyrazole substituents.

Pyrazolyl pyrazoline derivatives were found to possess potent activities such as anti-inflammatory,[8] antimicrobial,[9] antiallergic,[10] antidiabetic,[11] cardiovascu-

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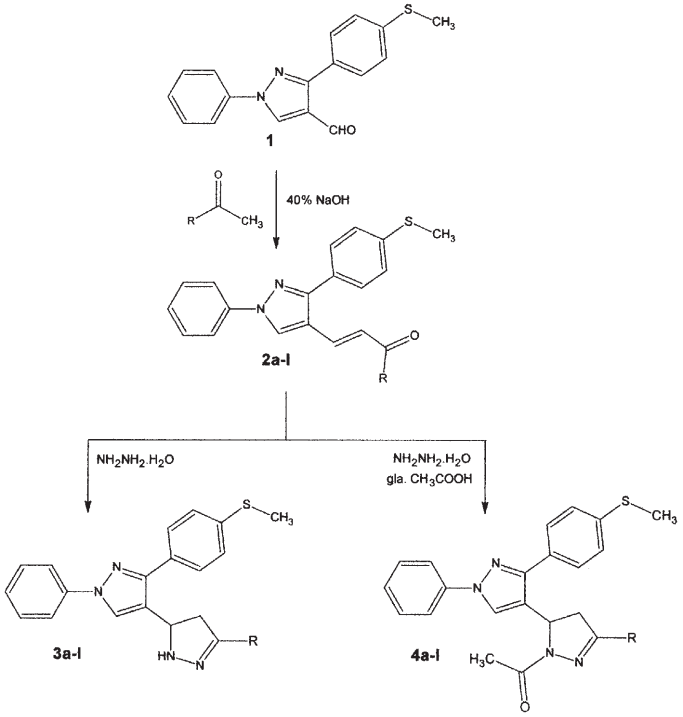
lar[12] and diuretic,[13] *etc*. The synthesis of a series of 3-aryl-5-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-4,5-dihydro-(1*H*)-pyrazoles **3a–l** and 1-acetyl-3-aryl-5-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-4,5-dihydro-(1*H*)-pyrazoles **4a–l** and their antitubercular and antimicrobial screening are reported.

3-Aryl-5-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-4,5-dihydro-(1*H*)-pyrazoles **3a–l** and 1-acetyl-3-aryl-5-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-4,5-dihydro-(1*H*)-pyrazoles **4a–l** were synthesized by treating 1-aryl-3-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-2-propen-1-ones **2a–l** with hydrazine hydrate and hydrazine hydrate in glacial acetic acid, respectively (Scheme 1).

The structures of the synthesized compounds **2a–l**, **3a–l** and **4a–l** were assigned on the basis of elemental analysis (Table I) as well as IR, ^{1}H NMR, and mass spectral data (Table II). The bioassay indicated most of the synthesized compounds possessed significant growth promoting effects on various microbes. Under identical conditions, standard antibiotics showed zones of inhibition, such as ampicillin 20–24 mm, amoxicillin 21–25 mm, norfloxacin 18–25 mm, benzyl penicillin 15–20 mm, against bacterial strains and griseofulvin showed zones of inhibition of 18–24 mm against *Aspergillus niger*. None of the tested compounds showed significant *in vitro* antituberculosis activity at the 6.25 μg/mL level (MIC rifampin 0.25 μg/mL).



Scheme 1.

EXPERIMENTAL

TLC was used to assess the reactions and the purity of the synthesized compounds. The melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8400 instrument in a KBr disc and only noteworthy absorption levels (cm^{-1}) are listed, ^1H NMR spectra on a Brucker AC-300 MHz FT NMR using TMS as the internal standard (chemical shifts in δ, ppm), and mass spectra on a Jeol D-300 spectrophotometer. All the compounds gave satisfactory elemental analysis.

*Synthesis of 1-(*p*-chlorophenyl)-3-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-2-propen-1-one (**2b**)*

To a solution of 1-phenyl-3-[*p*-(methylthio)phenyl]-4-formylpyrazole (2.94 g, 0.01 mol) and *p*-chloroacetophenone (1.5 g, 0.01 mol) in ethanol (25 ml), 40 % NaOH was added until the solution became alkaline. The reaction mixture was stirred for 24 h. The contents were poured onto crushed ice, the product isolated and crystallized from ethanol. Yield 58 %; m.p. 134 ºC. Anal. Calcd. for $C_{25}H_{19}ClN_2OS$; Required: C 69.68; H, 4.44; N, 6.50 %; Found: C, 69.65; H, 4.42; N, 6.48 %. IR(KBr, cm^{-1}): 2966 (C–H str., aromatic), 1660 (C=O str.), 1502 (CH=CH str.), 1215 (C–N str.), 686 (C–Cl, str.). ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 2.53 (*s*, 3H, Ar–SCH_3), 6.93–8.32 (*m*, 14H, Ar–H), 7.34–7.46 (*d*, 1H, C<u>H</u>=CH), 7.80–7.83 (*d*, 1H, CH=C<u>H</u>). The mass spectrum indicated the molecular ion peak at *m*/*z* 430 [M^+].

Similarly, the other compounds **2a–l** were prepared. Their characterization data are recorded in Table I and their spectral data in Table II.

*Synthesis of 3-(*p*-chlorophenyl)-5-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-4,5-dihydro-(1*H*)-pyrazole (**3b**)*

A mixture of 1-(*p*-chlorophenyl)-3-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-2-propen-1-one (4.30 g, 0.01 mol) and hydrazine hydrate (1 g, 0.02 mol) in 25 ml methanol was refluxed for 8 h. The reaction mixture was poured into ice cold water, the crude product isolated and crystallized from dioxane. Yield 65 %, m.p. 165 ºC; Anal. Calcd. for $C_{25}H_{21}ClN_4S$; Required: C, 67.48 %; H, 4.76 %; N, 12.59 %; Found: C, 67.43 %; H, 4.73 %; N, 12.56 %. IR (KBr, cm^{-1}): 3340 (N–H str.), 3074 (C–H str., aromatic), 1583 (C=N str.), 1095 (C–N str.), 617 (C–Cl, str.). ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 2.49 (*s*, 3H, Ar–SCH_3), δ 2.95–3.03 (*dd*, 1H, Ar–Hl), δ 3.36–3.45 (*dd*, 1H, Ar–Hm), δ 5.06–5.14 (*t*, 1H, Ar–Hk), δ 7.23–7.26 (*t*, 1H, Ar–Hc), δ 7.28–7.99 (*m*, 14H, Ar–H). The mass spectrum indicated the molecular ion peak at *m/z* 445 [M^+].

TABLE I. Characterization data of the compounds **3a–l**, **4a–l**

Compd.	R	M. f.	M. p./ºC	Yield/%	% of Nitrogen	
					Calcd.	Found
3a	C_6H_5–	$C_{25}H_{22}N_4S$	196	70	13.65	13.60
3b	4-Cl–C_6H_4–	$C_{25}H_{21}ClN_4S$	165	65	12.59	12.55
3c	4-Br–C_6H_4–	$C_{25}H_{21}BrN_4S$	102	85	11.45	11.42
3d	4-CH_3–C_6H_4–	$C_{26}H_{24}N_4S$	206	56	13.20	13.16
3e	4-OCH_3–C_6H_4–	$C_{26}H_{24}N_4OS$	170	60	12.72	12.70
3f	4-SCH_3–C_6H_4–	$C_{26}H_{24}N_4S_2$	118	78	12.27	12.24
3g	4-OH–C_6H_4–	$C_{25}H_{22}N_4OS$	108	62	13.14	13.10
3h	2-OH–C_6H_4–	$C_{25}H_{22}N_4OS$	240	65	13.14	13.11
3i	3,5-$(Br)_2$-4-OH–C_6H_2–	$C_{25}H_{20}Br_2N_4OS$	94	64	9.59	9.55
3j	4-NO_2–C_6H_4–	$C_{25}H_{21}N_5O_2S$	218	72	15.37	15.32

TABLE I. Continued

Compd.	R	M. f.	M. p./ºC	Yield/%	% of Nitrogen	
					Calcd.	Found
3k	3-NO_2–C_6H_4–	$C_{25}H_{21}N_5O_2S$	270	55	15.37	15.33
3l	C_5H_4N–	$C_{24}H_{21}N_5S$	160	78	17.02	17.03
4a	C_6H_5–	$C_{27}H_{24}N_4OS$	275	81	12.38	12.36
4b	4-Cl–C_6H_4–	$C_{27}H_{23}ClN_4OS$	125	59	11.50	11.45
4c	4-Br–C_6H_4–	$C_{27}H_{23}BrN_4OS$	102	62	10.54	10.51
4d	4-CH_3–C_6H_4–	$C_{28}H_{26}N_4OS$	106	57	12.01	12.00
4e	4-OCH_3–C_6H_4–	$C_{28}H_{26}N_4O_2S$	132	60	11.61	11.58
4f	4-SCH_3–C_6H_4–	$C_{28}N_{26}N_4OS_2$	118	85	11.24	11.20
4g	4-OH–C_6H_4–	$C_{27}H_{24}N_4O_2S$	108	61	11.96	11.92
4h	2-OH–C_6H_4–	$C_{27}H_{24}N_4O_2S$	140	70	11.96	11.93
4i	3,5-$(Br)_2$–4-OH–C_6H_2–	$C_{27}H_{22}Br_2N_4O_2S$	226	72	8.94	8.92
4j	4-NO_2–C_6H_4–	$C_{27}H_{23}N_5O_3S$	245	60	14.08	14.05
4k	3-NO_2–C_6H_4–	$C_{27}H_{23}N_5O_3S$	110	59	14.08	14.05
4l	C_5H_4N–	$C_{26}H_{23}N_5OS$	251	62	15.44	15.40

Similarly, the other compounds **3a–l** were prepared. Their characterization data are recorded in Table I and their spectral data in Table II.

TABLE II. IR and NMR spectral data of the compounds **3a–l**, **4a–l**.

Compd.	R	IR frequency in cm^{-1}			^1H NMR (in δ, ppm)	
		C–H str. alkane	C=N str.	–N–H str.	X	Ar–H
3a	C_6H_5–	2966	1608	3340	2.51 (*s*, 3H)	2.94–7.96 (*m*, 19H)
3b	4-Cl–C_6H_4–	2958	1606	3340	2.52 (*s*, 3H)	2.95–7.99 (*m*, 18H)
3c	4-Br–C_6H_4–	2955	1605	3345	2.53 (*s*, 3H)	2.96–7.93 (*m*, 18H)
3d	4-CH_3–C_6H_4–	2963	1608	3341	2.49 (*s*, 3H), 2.46 (*s*, 3H)	2.96–7.98 (*m*, 18H)
3e	4-OCH_3–C_6H_4–	2968	1612	3336	2.54 (*s*, 3H), 3.80 (*s*, 3H)	2.92–7.97 (*m*, 18H)
3f	4-SCH_3–C_6H_4–	2933	1601	3349	2.53 (*s*, 3H), 2.55 (*s*, 3H)	2.96–7.99 (*m*, 18H)
3g	4-OH–C_6H_4–	2976	1613	3350	2.48 (*s*, 3H)	2.94–7.94 (*m*, 19H)
3h	2-OH–C_6H_4–	2958	1616	3341	2.49 (*s*, 3H)	2.93–7.96 (*m*, 19H)
3i	3,5-$(Br)_2$-4-OH–C_6H_2–	2936	1620	3356	2.47 (*s*, 3H)	2.91–7.94(*m*, 17H)
3j	4-NO_2–C_6H_4–	2957	1619	3341	2.52 (*s*, 3H)	2.96–7.99 (*m*, 18H)
3k	3-NO_2–C_6H_4–	2945	1621	3334	2.53 (*s*, 3H)	2.92–7.96 (*m*, 18H)
3l	C_5H_4N–	2936	1613	3342	2.56 (*s*, 3H)	2.95–7.93 (*m*, 18H)
4a	C_6H_5–	2922	1563	3436	2.50 (*s*, 3H)	6.82–8.42 (*m*, 21H)
4b	4-Cl–C_6H_4–	2923	1564	3433	2.53 (*s*, 3H)	6.86–8.45 (*m*, 20H)
4c	4-Br–C_6H_4–	2945	1567	3456	2.51 (*s*, 3H)	6.82–8.46 (*m*, 20H)

TABLE II. Continued

Compd.	R	IR frequency in cm^{-1}			^1H NMR (in δ, ppm)	
		C–H str.–C=N alkane	str.	–N–H str.	X	Ar–H
4d	4-CH_3–C_6H_4–	2936	1558	3445	2.48 (*s*, 3H), 2.50 (*s*, 3H)	6.84–8.44 (*m*, 20H)
4e	4-OCH_3–C_6H_4–	2945	1562	3439	2.50 (*s*, 3H), 3.9 (*s*, 3H)	6.89–8.41 (*m*, 20H)
4f	4-SCH_3–C_6H_4–	2921	1556	3441	2.56 (*s*, 3H), 2.28 (*s*, 3H)	6.83–8.39 (*m*, 20H)
4g	4-OH–C_6H_4–	2931	1552	3425	2.49 (*s*, 3H)	6.81–8.38 (*m*, 21H)
4h	2-OH-C_6H_4–	2913	1563	3416	2.53 (*s*, 3H)	6.82–8.42 (*m*, 21H)
4i	3,5-$(Br)_2$–4-OH–C_6H_2–	2945	1564	3152	2.47 (*s*, 3H)	6.86–8.46 (*m*, 19H)
4j	4-NO_2–C_6H_4–	2910	1563	3429	2.54 (*s*, 3H)	6.85–8.39 (*m*, 20H)
4k	3-NO_2–C_6H_4–	2903	1552	3423	2.53 (*s*, 3H)	6.82–8.46 (*m*, 20H)
4l	C_5H_4N–	2914	1545	3433	2.52 (*s*, 3H)	6.84–8.43 (*m*, 20H)

*Synthesis of 1-acetyl-3-(*p-*chlorophenyl)-5-{1-phenyl-3-[*p-*(methylthio)phenyl]pyrazol-4-yl}-4,5-dihydro-(1*H*)-pyrazole (**4b**)*

A mixture of 1-(*p*-chlorophenyl)-3-{1-phenyl-3-[*p*-(methylthio)phenyl]pyrazol-4-yl}-2-propen-1-one (2.10 g, 0.01 mol), in 25 ml of ethanol, hydrazine hydrate (0.5 g, 0.01 mol) and glacial acetic acid (10 ml) was refluxed for 8 h. The content was poured onto ice. The product was isolated and crystallized from ethanol. Yield, 59 %. m.p. 125 ºC. Anal. Calcd. for $C_{27}H_{23}ClN_4OS$; Required: C, 66.59 %; H, 7.28 %; N, 11.50 %. Found: C, 66.55 %; H, 7.25 %; N, 11.45 %. IR (KBr, cm^{-1}): 3433 (N–H str.), 3053 (C–H str., aromatic), 1564 (C=N str.), 1033 (C–N str.), 760 (C–Cl, str.). ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 2.44 (*s*, 3H, –$NCOCH_3$), δ 2.49 (*s*, 3H, Ar–SCH_3), δ 3.02–3.09 (*dd*, 1H, Ar–Hl), δ 3.54–3.64 (*dd*, 1H, Ar–Hm), δ 5.83–5.88 (*dd*, 1H, Ar–Hk), δ 6.88–7.76 (*m*, 14H, Ar–H). The mass spectrum indicated the molecular ion peak at *m/z* 488 [M^+].

Similarly, the other compounds **4a–l** were prepared. Their characterization data are recorded in Table I and their spectral data in Table II.

RESULTS AND DISCUSSION

Antitubercular activity.

The antitubercular evaluation of the compounds was carried out at the Tuberculosis Antimicrobial Acquistition Co-ordinating Facility (TAACF), USA. All the compounds were screened against *Mycobacterium tuberculosis* strain $H_{37}Rv$ at a concentration of 6.25 μg/mL in BACTEC 12B medium using the ALAMAR radiometric system.

The antitubercular activity data were compared with the standard drug Rifampin at 0.25 μg/mL concentrations, which showed 98 % inhibition (Table III).

Antimicrobial activity.

The antimicrobial activity was assayed using the cup-plate agar diffusion method[14] by measuring the zone of inhibition in mm. All the compounds were

TABLE III. Antitubercular and antimicrobial screening results for compounds **3a–l**, **4a–l**.

Compd.	% Inhibition antitubercular activity	Zones of inhibition				
		Antimicrobial activity				Antifungal activity
		B. coccous	*B. subtilis*	*E. coli*	*P. vulgaris*	*A. niger*
3a	25	13	13	10	11	14
3b	36	21	17	19	10	17
3c	24	12	16	12	13	13
3d	29	22	14	11	17	18
3e	86	10	10	8	18	14
3f	18	08	08	17	12	10
3g	42	09	12	16	19	13
3h	00	10	21	12	13	18
3i	55	14	13	14	20	17
3j	00	16	14	13	16	14
3k	25	17	17	10	10	21
3l	10	12	18	21	14	16
4a	35	11	10	12	13	10
4b	42	08	16	10	18	17
4c	36	13	14	12	11	12
4d	86	12	12	14	10	21
4e	55	13	23	16	14	11
4f	18	18	16	13	18	18
4g	42	16	13	17	08	16
4h	00	17	18	19	17	21
4i	11	13	17	16	19	17
4j	35	17	11	17	16	23
4k	10	11	13	18	17	12
4l	56	18	18	14	23	10
Ampicillin	–	20	24	22	21	00
Amoxicillin	–	21	24	25	25	00
Norfloxacin	–	18	17	24	25	00
Benzyl penicillin	–	20	18	18	15	00
Griseofulvin	–	00	00	00	00	24

screened *in vitro* for their antimicrobial activity against the bacterial strains *Bacillus coccous*, *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris* and the fungi *Aspergillus niger* at a concentration of 40 μg/mL. The standard drugs ampicillin, amoxicillin, norfloxacin, benzyl penicillin and griseofulvin were used for compa-

rison purposes. The results are given in Table III, from where it can be seen that the compounds **3b**, **3d**, **3k**, **4f**, **4j** and **4l** were active against *B. coccous*, the **3b**, **3f**, **3k**, **3l**, **4e**, **4g**, **4i** and **4l** against *B. subtilis*, the compounds **3b**, **3f**, **3l**, **4g**, **4h**, **4j** and **4k** against *E. coli*, the compounds **3d**, **3e**, **3g**, **3i**, **4b**, **4f**, **4g**, **4h** and **4l** against *P. vulgaris* and the compounds **3b**, **3d**, **3h**, **3i**, **3k**, **4b**, **4d**, **4g**, **4h** and **4i** display maximum activity against *A. niger*.

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И З В О Д

СИНТЕЗА И СЕЛЕКТИВНА ИНХИБИТОРСКА АНТИТУБЕРКУЛИНСКА И АНТИБАКТЕРИЈСКА АКТИВНОСТ ДЕРИВАТА 1-АЦЕТИЛ-3,5-ДИФЕНИЛ-4,5-ДИХИДРО-(1*H*)-ПИРАЗОЛА

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Нова једињења 1-арил-3-{1-фенил-3-[*p*-(метилтио)фенил]-пиразол-4-ил}-2-пропен-1-они **2a–l** добијена су кондензацијом 1-фенил-3-[*p*-(метилтио)фенил]-4-формилпиразола **1** са различитим арилкетонима. Једињења **2a–l** у реакцији са хидразинхидратом дала су 3-арил-5-{1-фенил-3-[*p*-(метилтио)фенил]-пиразол-4-ил}-4,5-дихидро-(1*H*)-пиразоле **3a–l** и у присуству хидразинхидрата у глацијалној сирћетној киселини 1-ацетил-3-арил-5-{1-фенил-3-[*p*-(метилтио)фенил]-пиразол-4-ил}-4,5–дихидро-(1*H*)-пиразоле **4a–l**. Ова једињења су тестирана *in vitro* на антитуберкулинску и антибактеријску активност. *In vitro* антигљивична и антибактеријска активност синтетизованих једињења испитивана је према *Mycobacterium tuberculosis* $H_{37}RV$ (ATCC 27924) у BACTEC 12B средини коришћењем ALAMAR радиометријског система. Антимикробна активност *in vitro* тестирана је према *Bacillus coccous*, *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, као и антигљивична активност према *Aspergillus niger*. Структура синтетизованих једињења дефинисана је на основу елементалне анализе, IR, ^{1}H NMR и масеноспектрометријских података.

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