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Synthesis, characterization and Screening of 1,2,4 Triazole Derivative Compounds for Its Antimicrobial Activity

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A series of 3-benzoylsulfanyl derivatives of 4-methyl-1,2,4-triazole were synthesized by acylation of starting triazole -3-thiol with appropriately substituted benzoyl halide. All members of the set were evaluated for in vitro antimicobacterial activity against *Psuedomonas aerogenosa, Escherichia coli, Bacillus subtilis, Bacillus pumitis* and antifungal acivity against *A.niger, C.albicans*. The activities were expressed as the minimum inhibitory concentration. The compound exhibited only a moderate or slight antimycobacterial activity. The structures of the newly synthesized compounds were characterized by IR, ^{1}H NMR and elemental analysis.

Keyword: Triazoles, Acylation,Benzoyl Halides, Anti-microbial Activity

1. Introduction

Triazoles derivatives have been reported to exhibit antibacterial, antifungal and antimycobacterial[6,10] properties. The synthesis of these heterocycles has received considerable attention in recent years. As part of our program aimed at developing new biologically active compounds, in this work we report synthesis of some new monosubstituted -1,2,4 triazole-3-benzoylsufanyl derivatives through acylation as shown in the scheme.

2. Materials and Methods:

All the chemicals used for the study were obtained from Sigma Aldrich and Loba-e. Melting Points were determined on a open glass capillary tubes using Lab India Visual Melting Point Apparatus which was uncorrected. IR spectra were recorded as thin films on a KBr pellets with a Shimadzu spectrophotometer.1H NMR was measured with a Bruker spectrophotometer at 300 MHz using TMS as internal standard. DMSO-D_6 was used as a solvent.

2.1. General Procedure for Preparation of Compounds.

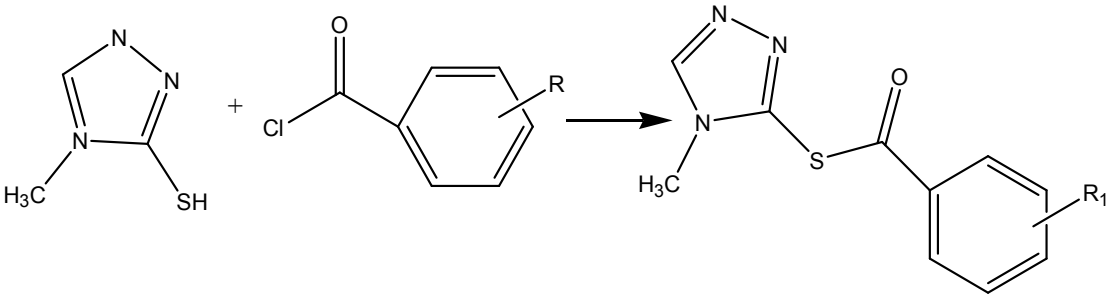
Step I: 4-methyl-1,2,4-triazole-3-thiol (0.69g, 6mmol) in dry N,N-dimethylformamide (DMF) (3ml) was added to a solution of sodium (0.14g, 6mmol) in dry methanol(2ml).

Step II: After 10 min of stirring at room temperature, benzoyl halide (6mmol) was added. The resultant suspension was stirred with $CaCl_2$ cap at room

temperature for 1-8hours and it was refluxed. The course of reaction was monitored by TLC.

Step III: In some cases, in order to accelerate the reaction course, the mixture was heated at 50-80^0 C. The reaction mixture was poured into an ice bath. The solid was filtered off, washed with cold water and air dried. The crude product was purified by crystallization with an absolute alcohol.

2.2. Scheme of the Synthesis



4-methyl,-1,2,4-triazole -3-thiol benzoyl halide 3-benzoylsulfanyl-4-methyl-1, 2, 4-triazole

benzoylsulfanyl-4-methyl-.1,2,4 triazole(D_1)

IR (cm^{-1}) 3067, 2833(CH), 1728(CO), 1686(CS);^{1}HNMRδ7.49,7.54(m,4H,Ar), 2.56 (s,3H,CH_3). Anal. $C_{10}H_9N_3SO$ (C: 53.97,H: 4.95,N: 19.08,S: 13.06,O: 8.90)

3(4-nitrobenzoylsulfanyl)-4-methyl-1,2,4-triazole(D_2)

IR(cm^{-1})2990,3116(CH),1718(CO),1527(CS);^{1}HNMRδ8.06,8.17(m,4H,ArH),2.8(s,3H,CH_3).Anal.$C_{10}H_8N_4SO_3$ (C:40.47,H:3.46, N: 21.09, S: 17.78,O: 15.74)

3(3-nitrobenzoylsulfanyl)-4-methyl-1,2,4-triazole (D_3)

IR(cm^{1})2929,3090(CH),1723(CO),1533(CS);^{1}HNMRδ8.28-(m,4H,ArH),2.92 (s,3H,CH_3).Anal. $C_{10}H_8N_4SO_3$ (C: 49.47, H: 4.54, N: 17.87, S: 8.34, O: 21.34)

3-(3-chlorobenzoylsulfanyl)-4-methyl-1,2,4-triazole (D_4)

IR(cm^{1})2921,2994,3077(CH),1696(CO), 1569,1597(CS);^{1}HNMRδ7.99(m,4H,ArH),2.59(s,3H,CH_3).Anal.$C_{10}H_8N_3SOCl$ (C:47,H:3.79,N: 17.75, S: 10.77,O: 6.53)

3-(4-bromobenzoylsulfanyl)-4-methyl-1, 2, 4-triazole(D_5)

IR(cm^{-1})2817(CH),1685(CO),1563(CS): ^{1}HNMRδ7.8(m,4H,ArH), 3.01(s,3H,CH_3) Anal. $C_{10}H_8N_3SOBr$ (C: 42.79, H: 3.19, N: 11.00, S: 8.73, O: 8.04)

3-(3-bromobenzoylsulfanyl)-4-methyl-1, 2, 4-triazole(D_6)

IR(cm^{1})2889,3035,3291(CH),1696(CO), 1564(CS);^{1}HNMRδ8.06(m,4H,ArH),2.93(s,3H,CH_3).Anal.$C_{10}H_8N_3SOBr$ (C:41.78, H: 2.52, N: 12.13, S: 10.22, O: 5.66)

3-(3-methoxybenzoylsulfanyl)-4-methyl-1,2,4-triazole(D_7)

IR(cm^{1})2925,3079(CH),1713(CO),1602, 1462(CS):^{1}HNMR7.58(m,4H,ArH)

3.6(s,3H,CH_3).Anal.$C_{11}H_8N_3SO_2$ (C:53.56, H:4.43, N:16.47, S:12.00, O: 14.74)

3-(2-bromobenzoylsulfanyl)-4-methyl-1,2,4-triazole(D_8)

IR(cm^{-1})2814,2923(CH),1682(CO),1586(CS);^{1}HNMRδ7.52(m,4H,ArH),3.45 (s,3H,CH_3).Anal.$C_{10}H_8N_3SOBr$ (C: 1.79,H: 2.53, N: 12.18, S: 10.97 , O: 4.74)

3-(2-nitrobenzoylsulfanyl)-4-methyl-1,2,4-triazole (D_9)

IR(cm^{-1}) 2924 (CH), 1735, 1678(CO), 1530(CS);^{1}HNMRδ 7.88(m,4H,ArH), 3.45 (s,3H,CH_3).Anal. $C_{10}H_8N_4SO_3$ (C: 47.27, H: 3.06, N: 18.60, S: 8.36, O: 23.74)

3-(3-methoxybenzoylsulfanyl)-4-methyl-1,2,4-triazole(D_{10})

IR (cm^{-1}) 2936 (CH), 1692(CO), 1589, 1467(CS);^{1}HNMRδ 7.4(m, 4H, ArH), 3.8 (s, 3H, CH3).Anal. $C_{11}H_8N_3SO_2$ (C: 62.18, H: 5.20, N: 12.38, S: 11.31, O: 8.81)

3-(4-chlorobenzoylsulfanyl)-4-methyl-1,2,4-triazole (D_{11})

IR (cm^{-1}) 2842, 2927 (CH), 1687(CO), 1587, 1424(CS):^{1}HNMRδ 7.97(m, 4H, ArH), 3.51 (s, 3H, CH3).Anal. C: 50.73,H: 3.21, N: 15.57, S: 8.21, O: 7.95)

Table 1: List of Physical Constant

Compound	Mol.Formula	Mol.Wt	M.P(^{0}C)	Yield %	R_f Value
D_1	$C_{10}H_9N_3SO$	219.26	119^0-121^{0}C	54%	0.68
D_2	$C_{10}H_8N_4O_3S$	264.26	89^0-91^{0}C	62%	0.64
D_3	$C_{10}H_8N_4O_3S$	264.26	(B.P)60^0-62^{0}C	66%	0.74
D_4	$C_{10}H_8N_3OSCl$	253.71	114^0-116^{0}C	38%	0.56
D_5	$C_{10}H_8N_3OSBr$	298.16	89^0-91^{0}C	53%	0.72
D_6	$C_{10}H_8N_3OSBr$	298.16	59^0-61^{0}C	59%	0.56
D_7	$C_{11}H_8N_3O_2S$	246.26	112^0-114^{0}C	49%	0.74
D_8	$C_{10}H_8N_3OSBr$	298.16	79^0-81^{0}C	42%	0.70
D_9	$C_{10}H_8N_4O_3S$	276.27	99^0-101^{0}C	54%	0.64
D_{10}	$C_{11}H_8N_3O_2S$	246.26	69^0-71^{0}C	32%	0.62
D_{11}	$C_{10}H_8N_3OSCl$	253.71	160^0-162^{0}C	56%	0.60

4. Antimicrobial Screening:

The synthesized compounds were evaluated for the invitro antibacterial activity against Gram –positive bacteria: *Bacillus pumillis* and *Bacillus subtilis*. Gram –negative bacteria: *Escherichia coli, Pseudomonas aeruginosa*. The compounds were also tested invitro antifungal activity against *Candida albicans* and *Asperigillus niger* by disc diffusion method at 2µgm/ml, 5µgm/ml, 10µgm/ml concentration of the test compound. Amikamycin was used as a standard antibacterial agent Clotrimazole was used aas antifungal agent. The zone of inhibition was measured and shown on table-2 and 3

Table 2: Antibacterial activity (zone of inhibition in mm)

S.No.	Compounds	*Psuedomonas aerogenosa*			*Escherichia coli*			*Bacillus subtilis*			*Bacillus pumitis*		
		2	5	10	2	5	10	2	5	10	2	5	10
1.	**D_1**	6.20	7.13	8.16	6.81	7.13	8.90	6.06	6.20	7.24	6.90	7.33	8.36
2.	**D_2**	8.16	7.23	10.16	7.30	8.14	9.20	7.03	8.40	9.93	8.20	9.16	0
3.	**D_3**	6.15	10.1	12.12	6.33	9.26	10.28	8.24	10.2	8.33	6.30	7.20	10.2
4.	**D_4**	9.36	8.20	9.13	6.20	6.61	8.13	6.10	7.13	11.3	9.24	10.4	8.10
5.	**D_5**	7.06	7.40	8.26	6.83	7.10	8.23	6.37	7.13	7.34	7.36	7.25	11.1
6.	**D_6**	6.10	7.10	8.00	7.10	7.06	9.24	0	6.23	8.13	6.10	6.25	0
7.	**D_7**	6.20	10.8	11.43	6.16	6.60	7.06	0	7.43	9.30	6.20	6.76	8.14
8.	**D_8**	7.24	6.86	6.40	6.02	8.60	6.76	6.23	8.08	7.13	6.10	8.33	7.18
9.	**D_9**	6.23	7.16	7.16	6.04	8.80	7.03	7.26	6.10	10.3	6.03	6.70	8.26
10.	**D_{10}**	6.10	6.12	6.96	0	6.36	6.76	6.10	6.20	7.76	7.04	7.70	8.13
11.	**D_{11}**	6.63	7.10	7.20	0	6.34	7.30	6.04	6.20	7.90	6.10	8.20	9.14
Std	**Amikamycin**	9.25	11.5	13	7.68	9.01	10.75	8.90	10.08	9.77	8.80	11	12.02

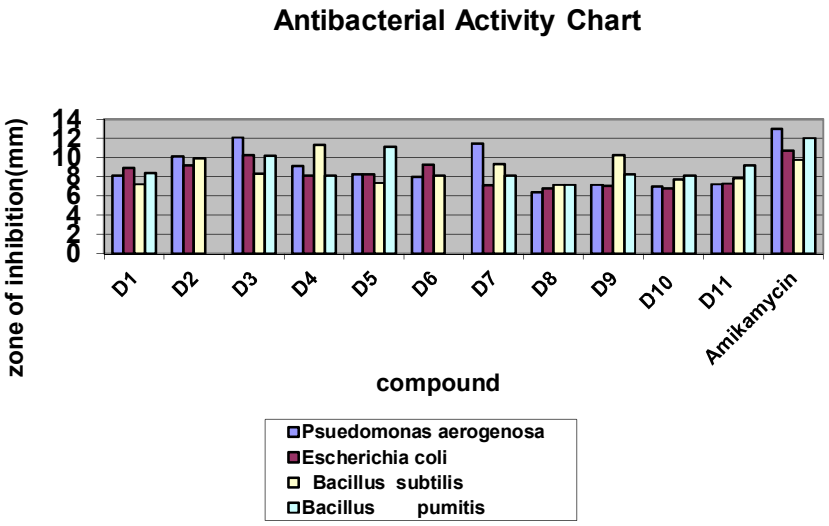
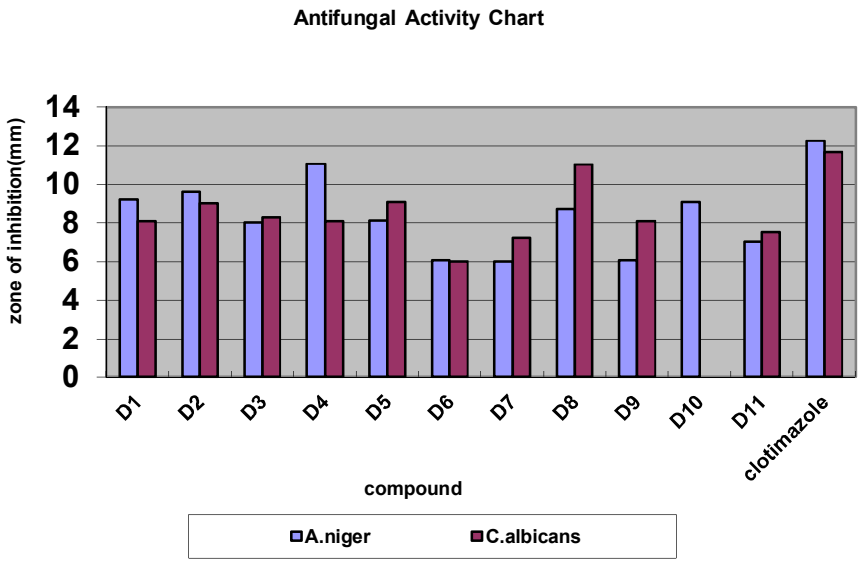


Table 3: Antifungal activity(zone of inhibition in mm)

S.N.	Compounds	A.niger			C.albicans		
		2	5	10	2	5	10
1.	D_1	6.10	8.30	9.20	6.86	7.03	8.10
2.	D_2	8.03	9.23	9.60	7.12	8.00	9.02
3.	D_3	7.13	7.44	8.01	8.13	8.22	8.28
4.	D_4	10.13	10.88	11.06	7.05	7.34	8.10
5	D_5	7.20	8.02	8.12	7.16	8.60	9.10
6	D_6	0	6.00	6.04	0	0	6.00
7	D_7	0	0	6.00	6. 16	6.46	7.21
8	D_8	6.13	7.01	8.72	9.02	10.16	11.02
9	D_9	0	6.02	6.04	7.32	7.44	8.08
10	D_{10}	7.06	8.10	9.08	0	0	0
11	D_{11}	6.04	6.30	7.03	6.14	7.00	7.55
Std	Clotrimazole			**12.24**			**11.67**



5. Result and Discussion

Purity of the compound was determined by TLC on silica gel G plates. The spots were detected by exposure to iodine vapours. Synthesized compound were detected by spectral analysis (FTIR, ^{1}H-NMR). sSS Synthesized compound of substituted 3-benzoylsulfanyl-4-methyl-1, 2, 4 triazole were tested for the antibacterial activity against gram +ve (*Bacillus subtilis, Bacillus pumitis*) and gram –ve (*Pseudomonas aerogenosa, E.coli)* the tested compound D_3, D_7 showed good antibacterial activity against *Pseudomonas aerogenosa*. The tested compound D_2, D_4, D_9 showed good activity against to *Bacillus subtilis*. The tested compound D_3 to *Escherichia coli* and D_3, D_5 showed good activity towards *Bacillus pumitis* compared to standard drug Amikamycin.

Synthesized compound of substituted 3-benzoylsufanyl-4-methyl-1,2,4-triazole were tested for the antifungal activity against *A.niger* and *C.albicans*. D_4 and D_8 showed better activity towards the fungus compared to activity showed by standard Clotrimazole. D_{10} did not show any activity.

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