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Research Article

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 1, 2, 4 TRIAZOLE DERIVATIVES CONTAINING THIAZOLIDINONE

VS. Wakale[1] and SR. Pattan[2*]

[1]Faculty of Pharmacy, Pravara Institutes of medical Sciences (DM), Loni-413 736, Ahmednagar, Maharashtra, India.

[2]Department of Pharmaceutical Chemistry, AbasahebKakade College of Pharmacy, Bodhegaon, Tal-Shevgaon-414 502, Dist- Ahmednagar, Maharashtra, India.

ABSTRACT

A series of 2-(4-substituted)-5-mercapto-4*H*-1,2,4-triazol-3-yl)phenol **(3a-3f)** and 3-(3-(2-hydroxyphenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)-2-substituted thiazolidin-4-one **(4a-4f)** was designed and synthesized. The synthesized compounds were characterized by IR, ^{1}H-NMR and elemental analysis. The synthesized compounds were evaluated for antibacterial activity by using cup plate agar diffusion method against *Escherichia coli* and *Staphylococcus aureus*, antifungal activity against *Aspergillusniger*and *Candida albicans*. Compounds **3c**, **4d**, and **4f** showed potent inhibition against all the bacterial and fungal strains.

Keywords: 1,2,4-triazole, Elemental analysis, Antibacterial, Antifungal activity.

INTRODUCTION

Five membered heteroatom containing heterocycles have turned out to be potential chemotherapeutic and pharmacotherapeutic agents. The synthesis of high nitrogen containing heterocyclic compounds has been increasing interest over the past decade because of their utility in various applications. The synthesis of triazole and their fused heterocyclic derivatives has attracted widespread attention due to their diverse biological and pharmacological activities, viz- antimicrobial[1-3], antitubercular[4], antioxidant[5], analgesic[6], anticancer[7], anticonvulsant[8-9], anti-inflammatory[10], antiviral[11], anthelmintic[12], antitumor[13], antidepressant[14] activities.

In the present paper, we discuss the synthesis, characterization and antimicrobial activities of the synthesized triazole derivatives. The structure assigned to compounds was substantiated by their analytical and other spectral data.

MATERIAL AND METHODS

Antimicrobial Activity[15]

The antimicrobial activities of newly synthesized compounds were determined by cup-plate diffusion method. All the compounds were tested for their antibacterial activity against *Escherichia coli* and*Staphylococcus aureus*using nutrient agar medium. Similarly the antifungal activity was carried out against*Aspergillusniger*and *Candida albicans*using Sabouraud-Dextrose agar.The concentration of sample compounds was 100µg/ml Norfloxacin and Griseofulvinwere used as standard drugs for antibacterial and antifungal activity respectively. Control test with solvents were performed for every assay but showed no inhibition of the microbial growth.

EXPERIMENTAL

Melting points were determined in open capillary method and are uncorrected. Purity of the compounds was checked on Silica Gel TLC plates. IR spectra were recorded on Thermo Nicolet IR 200 spectrophotometer using KBr disc method. ^{1}H

NMR spectra were recorded on BRUKER AVANCE II 400 NMR Spectrometer, DMSO-d_6 as internal standards.Combustion analyses were found to be within the limits of permissible errors.

General procedure for synthesis of 2-hydroxy benzohydrazide1[16]

A mixture of 0.1 mole (15.2 ml)methyl salicylate and 0.2 mole (10 ml) hydrazinehydrate were taken in a 250 ml round bottomed flask attached to a reflux condenser and refluxed with 50 ml of 95% abs ethanol for 15 hrs. The resultant mixture was concentrated in 250 ml beaker. It was cooled at room temperature and then kept it in refrigerator for 2 hrs. The solid mass thus separated out was filtered and dried. The same was recrystallized from ethanol.

General procedure for synthesis of 2(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-phenol 2[17-18]

The acid hydrazide**1** (0.01 mol) was added to absolute alcohol (50 mL), containing KOH (1.6 g) at room temperature. Carbon disulphide was added (2.3 g, 0.013 mol) and the mixture stirred at room temperature for 10 h. The mixture was diluted with ether (30 mL) and stirred for a further 1h. The potassium salt was used for the next stage without further purification. Hydrazine hydrate (99%) (0.02mol) was gradually added to the above potassium salt (0.01 mol) dissolved in water (20 mL) with stirring and the mixture was refluxed gently for 3 hr during which hydrogen sulphide evolved and the color of the reaction mixture changed to a dark green color, It was then cooled to 5 °C and acidified with conc. HCl to pH 1.00. A yellow solid separated out which was filtered, washed with water and crystallized from ethanol to make the triazole.

General procedure for synthesis of 2-(4-substituted)-5-mercapto-4*H*-1,2,4-triazol-3-yl)phenol3a-f[19]

A mixture of triazole**2** (0.01 mol) and the various substituted aldehydes (0.01 mol) in ethanol (25 ml) containing a drop of glacial acetic acid was refluxed for 2 hrs. The reaction mixture on cooling was filtered and purified by recrystallization from ethanol to give 3a-f.

3a: 2-(4-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)phenol

IR(KBr)cm^{-1}: 3417.24 (O-H str), 3057.58 (Ar C-H str), 2537.10 (S-H str), 1606.41(C=Nstr); ^{1}H NMR (DMSO, 400 MHz): δ (ppm) 13.51 (1H, SH), 9.97 (1H, N=CH)7.01-7.24 (4H, Ar-H),7.52-7.83 (4H, Ar-H), 5.35 (1H, OH).

3b: 2-(4-(4-hydroxybenzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)phenol

IR (KBr)cm^{-1}: 3422.02 (O-H str), 3052.76 (Ar C-H str), 2543.00 (S-H str), 1601.24 (C=Nstr).

3c: 2-(4-(4-methoxybenzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)phenol

IR (KBr)cm^{-1}: 3400.85 (O-H str), 3073.01 (Ar C-H str), 2551.12 (S-H str), 1608.34 (C=Nstr).

3d:4-((3-(2-hydroxyphenyl)-5-mercapto-4*H*-1,2,4-triazol-4-ylimino)methyl)-2-methoxyphenol

IR (KBr)cm^{-1}: 3265.86 (O-H str), 3030.59 (Ar C-H str), 2583.18 (S-H str), 1599.66 (C=Nstr);^{1}H NMR (DMSO, 400 MHz): δ (ppm) 13.05 (1H, SH), 9.56 (1H, N=CH) 6.91-7.24 (4H, Ar-H), 7.34-7.62 (3H, Ar-H), 5.35 (1H, OH), 3.83 (3H,CH_3).

3e: 2-(4-(2-chlorobenzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)phenol

IR (KBr)cm^{-1}: 3248.50 (O-H str), 3081.69 (Ar C-H str), 2552.33(S-H str), 1603.52 (C=Nstr).

3f: 2-(4-(furan-2-ylbenzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)phenol

IR (KBr)cm^{-1}: 3419.17 (O-H str), 3118.33 (Ar C-H str), 2527.66 (S-H str), 1606.41(C=Nstr); ^{1}H NMR (DMSO, 400 MHz): δ (ppm) 12.85 (1H, SH), 7.50 (1H, N=CH) 6.52-7.07 (4H, Ar-H), 7.24-7.75 (3H, Ar-H), 5.35 (1H, OH).

General procedure for synthesis of 3-(3-(2-hydroxyphenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)-2-substituted thiazolidin-4-one 4a-f:

A mixture of Schiff bases **3a-f** (0.01mol) and thioglycollic acid (0.01mol) dissolved in DMF (30 ml). The reaction mixture refluxed for 6 h and the solid obtained after removal of the solvent was crystallized from benzene to give **4a-f**.

4a:3-(3-(2-hydroxyphenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)-2-phenylthiazolidin-4-one

IR (KBr)cm^{-1}: 3346.85 (O-H str), 3056.62 (Ar C-H str), 2590.90(S-H str), 1613.16 (C=Ostr), 1573.63 (C=Nstr), 971.94 (C-S-C Str); ^{1}H NMR (DMSO, 400 MHz): δ (ppm) 11.87 (1H, SH), 7.18-7.48 (4H, Ar-H), 7.521-8.481(5H, Ar-H), 6.94 (1H, N-CH of methine), 3.85 (2H, CH_2).

4b:2-(4-hydroxyphenyl)-3-(3-(2-hydroxyphenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl) thiazolidin-4-one

IR (KBr)cm^{-1}: 3270.68 (O-H str), 3025.76 (Ar C-H str), 2567.75(S-H str), 1660.41 (C=O str), 1603.52 (C=N str), 842.74 (C-S-C Str); ^{1}H NMR (DMSO, 400 MHz): δ (ppm) 13.79 (1H, SH), 6.63-7.07 (4H, Ar-H), 7.24-7.78 (4H, Ar-H), 5.92 (1H, N-CH of methine), 3.95 (2H, CH_2).

4c:3-(3-(2-hydroxyphenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)-2-(4-methoxyphenyl) thiazolidin-4-one

IR (KBr)cm^{-1}: 3411.46 (O-H str), 2982.37 (Ar C-H str), 2576.71(S-H str), 1692.23 (C=O str), 1528.31 (C=N str), 1026.83 (C-O-C Str), 852.03 (C-S-C Str); ^{1}H NMR (DMSO, 400 MHz): δ (ppm) 12.68 (1H, SH), 6.37-6.40 (4H, Ar-H), 7.26-7.65 (4H, Ar-H), 5.75 (1H, N-CH of methine), 2.56 (2H, CH_2).

4d:2-(4-hydroxy-3-methoxyphenyl)-3-(3-(2-hydroxyphenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)thiazolidin-4-one

IR (KBr)cm^{-1}: 3531.02 (O-H str), 2921.63 (Ar C-H str), 2577.40 (S-H str), 1655.59 (C=O str), 1592.91 (C=N str), 1030.77 (C-O-C Str), 900.59 (C-S-C Str); ^{1}H NMR (DMSO, 400 MHz): δ (ppm) 11.69 (1H, SH), 6.64-7.39 (4H, Ar-H), 7.46-8.38 (4H, Ar-H), 6.84 (1H, N-CH of methine), 3.96 (2H, CH_2), 3.74-3.88 (3H, CH_3).

4e:2-(2-chlorophenyl)-3-(3-(2-hydroxyphenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl) thiazolidin-4-one

IR (KBr)cm^{-1}: 3422.06 (O-H str), 3062.33 (Ar C-H str), 2584.15 (S-H str), 1728.87 (C=O str), 1606.41 (C=N str),926.62 (C-S-C Str); ^{1}H NMR (DMSO, 400 MHz): δ (ppm) 12.09 (1H, SH), 7.29-7.74 (4H, Ar-H), 7.91-8.21 (4H, Ar-H), 6.95 (1H, N-CH of methine), 3.84 (2H, CH_2).

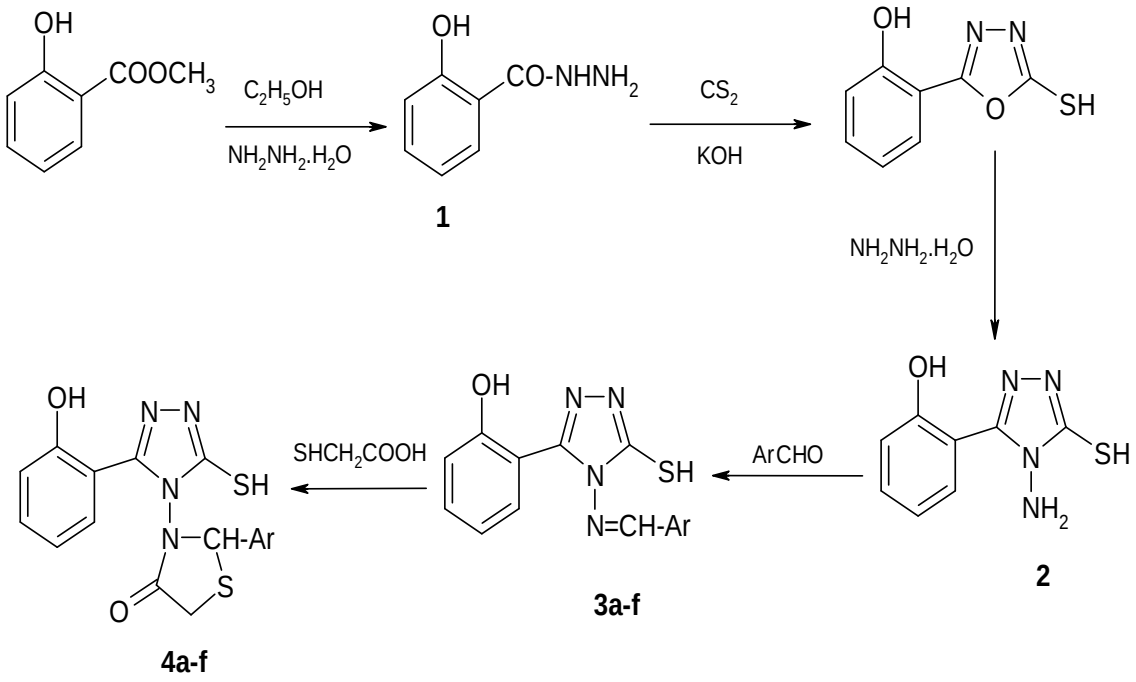
4f:2-(furan-2-yl)-3-(3-(2-hydroxyphenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl) thiazolidin-4-one

IR (KBr)cm^{-1}: 3517.52 (O-H str), 2925.20 (Ar C-H str), 2494.66(S-H str), 1716.34 (C=O str), 1603.52 (C=N str), 1150.33 (C-O-C Str), 754.99 (C-S-C Str); ^{1}H NMR (DMSO, 400 MHz): δ (ppm) 10.01 (1H, SH), 7.01-8.11 (7H, Ar-H), 6.89 (1H, N-CH of methine), 3.39 (2H, CH_2).

RESULT AND DISCUSSION

Synthesis of 2-(4-substituted)-5-mercapto-4*H*-1,2,4-triazol-3-yl)phenol (3a-3f) and 3-(3-(2-hydroxyphenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)-2-substituted thiazolidin-4-one (4a-4f) under refluxing condition required 2h and 6h, respectively, and higher product yields making it superior method. The IR spectra of the derivatives showed absorption band at 3248-3422 cm^{-1} due to the OH functional group and the weak absorption band around 2537-2552 cm^{-1} due to the SH group. An absorption band observed for all the synthesized compounds in the range of 2925-3082 cm^{-1} may be attributed to aromatic stretching vibration, while that seen at 1599-1608 cm^{-1} corresponds to C=N linkage. Thus, the formation of iminomethine functional group in the compound was indicated. In ^{1}H NMR spectrum a singlet at δ 13.51 due to -SH protons, a multiplet at 7.01-7.83 due to aromatic and singlet at 9.97 due to –N=CH protons. The IR, ^{1}H NMR, and elemental analysis supported the structure of various synthesized 1,2,4-triazole derivatives.

The synthesized compounds have been evaluated for antimicrobial activity by cup-plate diffusion method. Compounds **3c**, **4d**, and **4f** showed potent inhibition against all the bacterial and fungal strains. Compounds **3d**, **4a** and **4c** were activeagainst *Escherichia coli* and *Staphylococcus aureus*, Compounds **3f** and **4b** were active against *Aspergillusniger*and *Candida albicans*, which were approximately equipotent in activity and comparable to that of Norfloxacin and Griseofulvin. Remaining compounds showed moderate to good antimicrobial activity.



Ar- a= -C_6H_5, b=4-OHC_6H_4, c=4-$OCH_3C_6H_4$, d=3-OCH_3, 4-OHC_6H_3, e= 2-ClC_6H_4, f= -OC_4H_3

Scheme-I

Table 1: Physical and Analytical Data of Synthesized compounds

Comp.	Mol. Formula	Mol. Wt.	M. P. ^{0}C	R_f Value	Yield %	Elemental analysis Calcd. (Found)		
						C	H	N
3a	$C_{15}H_{12}N_4OS$	296	210-12	0.54	72	60.79 (60.82)	4.08 (4.10)	18.91 (18.87)
3b	$C_{15}H_{12}N_4O_2S$	312	219-21	0.48	66	57.68	3.87	17.94
3c	$C_{16}H_{14}N_4O_2S$	326	197-99	0.58	63	58.88	4.32	17.17
3d	$C_{16}H_{14}N_4O_3S$	342	231-33	0.68	80	56.13 (56.21)	4.12 (4.19)	16.36 (16.32)
3e	$C_{15}H_{11}ClN_4OS$	330	285-87	0.42	74	54.46	3.35	16.94
3f	$C_{13}H_{10}N_4O_2S$	286	180-82	0.52	68	54.54 (54.49)	3.52 (3.55)	19.57 (19.62)
4a	$C_{17}H_{14}N_4O_2S_2$	370	225-27	0.60	65	55.12 (55.16)	3.81 (3.86)	15.12 (15.08)
4b	$C_{17}H_{14}N_4O_3S_2$	386	188-90	0.47	78	52.84 (52.78)	3.65 (3.60)	14.50 (14.56)
4c	$C_{18}H_{16}N_4O_3S_2$	400	158-60	0.40	73	53.99 (53.94)	4.03 (4.10)	13.99 (13.89)
4d	$C_{18}H_{16}N_4O_4S_2$	416	206-09	0.71	67	51.91 (51.95)	3.87 (3.91)	13.45 (13.51)
4e	$C_{17}H_{13}ClN_4O_2S_2$	404	186-88	0.63	60	50.43 (50.51)	3.24 (3.28)	13.84 (13.89)
4f	$C_{15}H_{12}N_4O_3S_2$	360	196-98	0.59	79	49.99 (50.05)	3.36 (3.40)	15.55 (15.51)

Table 2: Antimicrobial activity of synthesized compounds (3a-f, 4a-f)

Comp.	Zone of inhibition at 100 µg/ml (in mm)			
	Antibacterial		Antifungal	
	E. coli	*S.* aureus	*A.* niger	*C.* albicans
3a	14	16	12	13
3b	12	15	16	15
3c	**18**	**20**	**21**	**20**
3d	**20**	**21**	13	16
3e	13	12	15	17
3f	15	18	**20**	**19**
4a	**20**	**22**	12	15
4b	13	16	**22**	**21**
4c	**21**	**22**	15	16
4d	**17**	**20**	**23**	**20**
4e	15	16	17	15
4f	**19**	**21**	**22**	**19**
Norfloxacin	**21**	**23**	--	--
Griseofulvin	--	--	**24**	**22**

CONCLUSION

This study reports the synthesis, characterization and antimicrobial activity of series of triazole derivatives. The synthesized compounds were subjected to spectral analysis such as IR, ^{1}H-NMR and Elemental analysis to confirm the structure. All the analytical details show satisfactory results. All the compounds were tested for antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* using Norfloxacin as standard drug and antifungal activity was performed against *Aspergillusniger*and *Candida albicans* using Griseofulvinas standard drug. The screening results revealed that most of the compounds showed promising antimicrobial activity.

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