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Microwave assisted synthesis and characterization of some new triazole derivatives

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ABSTRACT

The reaction of 4-chlorobenzoic acid **(1)** with thiocarbohrdrazide **(2)** by fussion method to get 4-amino-5-(4-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol **(3)**. Treatment of compound **(3)** with various aromatic aldehydes in presence of dry benzene to yield 4-(benzylidene amino)-5-(4-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol (4a-e) respectively. which on reaction with acetyl chloride and triethylamine in presence of dry benzene afforded 1-[3-(4-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl]-4-phenylazetidin-2-one (5a-e). The purity of the compounds was checked by TLC. All newly synthesized compounds were characterized on the basis of IR, ^{1}HNMR, mass spectral data and elemental analysis.

KEYWORDS

4-chlorobenzoicacid;
Triazoles;
Azetidin-2-one
Antimicrobial activity.

INTRODUCTION

1,2,4-Triazole derivatives possess potent biological activities such as pesticidal, herbicidal, fungicidal[1,2], antimicrobial[3,4], anticonvulsants and anti-inflammatory[5] activities. The earlier studies indicated that thiol grouping at position-5 enhance antimicrobial property of the triazoles. In view of this and in continuation of our research on the synthesis of biologically active heterocycles[6,7] we have now synthesized various heterocycles derived from 4-chlorobenzoic acid to evaluate their antimicrobial activity. The target molecule **(3)** was synthesized by reacting 4-chlorobenzoic acid with thiocarbohydrazide by fusion method. The compound **(3)** was converted to the corresponding Schiff's base (4a-e) which was then reacted with acetyl chloride and trietylamine in presence of dry benzene to yield the corresponding azetidines (5a-e). The purity of the compounds was checked by TLC. All newly synthesized compounds were characterized on the basis of IR, ^{1}HNMR, mass spectral data and elemental analysis. The synthesized compounds were studied for antimicrobial activity.

EXPERIMENTAL

The melting points were determined by open capillaries and are uncorrected. The purity of the compounds was checked by TLC. Infra red spectra were recorded on an FTIR-8400 Shimadzu Spectrophotometer Department of Pharmaceutical Chemistry, Karnataka College of pharmacy, Bidar. The ^{1}HNMR spectra were recorded ACF 200 Supercon-Switzerland NMR Spectraphotometer and were procured from central University Hyderabad; Chemical shifts were expressed in ppm (delta scale). Mass spectra were taken by using

Full Paper

LC-MS 2010 (SHIMADZU) Mass spectrometer from central University, Hyderabad.

Synthesis of 4-amino-5-(4-chlorophenyl)-4H-1, 2, 4-triazole-3-thiol. 3 (Coventional method)

A mixture of 4-chlorobenzoic acid (0.01 mole, 1.56g) and thiocarbohydrazide (0.01 mole, 1.06g) were heated till it melts. The mixture was maintained at this temperature for 30-40 min. It was cooled and treated with Sodium bicarbonate solution (10%, 10ml) to dissolve unreacted acid. The solid separated was collected by filtration, washed with water and recrystallized from ethanol. m.p, 231 ºC, elemental analysis found C (42.39%) H (3.11%) and N (24.72%) m.f $C_8H_7N_4SCl$, required C (42.37%) H (3.09%) and N (24.70%) The characterization data of compound **(3)** are recorded in TABLE 1.

TABLE 1 : Physical data of the synthesized compounds

Comp No.	R	M.P. (ºC)	Yield (%)		Time		Rf Value	Molecular Formula	Elemental analysis Found/(calculated) %		
			Conv	MW	Conv (hr)	MW (min)			C	H	N
3	--	231-233	67.12	82.33	1	6-7	0.59	$C_8H_7N_4SCl$	42.39 (42.37)	3.11 (3.09)	24.72 (24.70)
4a	C_6H_5	216-218	72.44	92.11	15-16	2-3	0.67	$C_{15}H_{11}N_4SCl$	57.23 (57.21)	3.52 (3.50)	17.80 (17.78)
4b	C_6H_4Cl (P)	212-214	62.33	89.21	15-16	2-3	0.50	$C_{15}H_{10}N_4SCl_2$	51.59 (51.57)	2.89 (2.87)	16.04 (16.02)
4c	C_6H_4OH (P)	214-216	62.12	91.01	15-16	2-3	0.64	$C_{15}H_{11}N_4OS$	54.46 (54.44)	3.35 (3.33)	16.94 (16.92)
4d	C_6H_4Br (P)	213-215	64.16	88.22	15-16	2-3	0.57	$C_{15}H_{10}BrClN_4S$	45.76 (45.74)	2.56 (2.54)	14.23 (14.20)
4e	$C_6H_4N(CH_3)_2$	221-223	70.34	95.34	15-16	2-3	0.63	$C_{17}H_{16}ClN_5S$	57.06 (57.03)	4.51 (4.49)	19.57 (19.55)
5a	C_6H_5	236-238	84.55	91.56	1	4-5	0.51	$C_{17}H_{13}N_4SOCl$	57.22 (57.20)	3.67 (3.67)	15.70 (15.67)
5b	C_6H_4Cl (P)	248-250	64.56	83.33	1	4-5	0.57	$C_{17}H_{12}N_4SOCl_2$	52.18 (52.15)	3.09 (3.07)	14.32 (14.30)
5c	C_6H_4OH (P)	245-247	72.76	88.61	1	4-5	0.63	$C_{17}H_{13}N_4SO_2Cl$	54.77 (54.77)	3.51 (3.51)	15.03 (15.03)
5d	C_6H_4Br (P)	244-246	69.42	84.76	1	4-5	0.60	$C_{17}H_{12}N_4SOClBr$	46.86 (46.84)	2.78 (2.75)	12.86 (12.84)
5e	$C_6H_4N(CH_3)_2$	251-253	76.31	94.21	1	4-5	0.61	$C_{19}H_{18}N_5SOCl$	57.04 (57.02)	4.54 (4.52)	17.51 (17.49)

All the compounds are crystallized from ethanol

Synthesis of 4-amino-5-(4-chlorophenyl)-4H-,2,4-triazole-3-thiol. 3 (Microwave method)

A mixture of 4-chlorobenzoic acid (0.01 mol, 1.56g) and thiocarbohydrazide (0.01 mol, 1.06g) was taken in a beaker, the reaction mixture was irradiated M767W (Electrolux) system (200 W) about 7- 8 min. Progress of reaction was monitored by TLC. After complication of the reaction it was treated with sodium bicarbonate solution (10%) 10ml. The triazole obtained was filtered, dried and recrystalized from ethanol. m.p, 231 ºC, elemental analysis found C (42.39%) H (3.11%) and N (24.72%) m.f $C_8H_7N_4SCl$, required C (42.37%) H (3.09%) and N (24.70%). The characterization data of compound **(3)** are recorded in TABLE 1.

4-(benzylideneamino)-5-(4-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol (Conventional method) (4a-e)

A mixture of 4-amino-5-(4-chlorophenyl)-4H-1,2,4-triazole-3-thiol (0.01 mole, 2.26 g) and substituted benzaldehyde (0.01mole, 1.06 g) in 30 ml of dry benzene and 100mg anhydrous zinc chloride was refluxed for 15-16 h. The excess of solvent removed by distillation the product obtained is filtered and washed with sodium bisulphide solution (10%, 10ml) to remove unreacted aldehyde and recrystalise with ethanol. The characterization data are given in TABLE 1

4-(benzylideneamino)-5-(4-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol (Microwave method) (4a-e)

A mixture of 4-amino-5-(4-chlorophenyl)-4H-1,2,4-triazole-3-thiol (0.01 mole, 2.26 g) and substituted benzaldehyde (0.01 mole 1.06 g) and 100 mg anhydrous zinc chloride was taken in a 50 ml beaker 10 ml methanol was added. The mixture was irradiated inside a microwave oven MC767W (Electrolux) (200w) for 2-3 min. Progress of reaction was monitored by TLC. After complication of the reaction, the contents were poured into crushed ice. The solid obtained was filtered off, washed with water and purified by recrystalisation from ethanol to get Schiff base (4a-e). The characterization data are given in TABLE 1

1-[3-(4-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl]-4-phenylazetidin-2-one (Conventional method) (5a-e)

To a solution of Schiff's base (0.002 mol, 0.5g) in dry benzene (30 ml) and a few drop of triethylamine was added. Then a solution of acetyl chloride (0.002 mol, 0.5g) added with stirring and refluxed for 1 hr. The triethylamine hydrochloride was obtained filtered off, washed several times with benzene. The filtrate and washing were mixed and concentrated under reduced pressure. The residue obtained was filtered, dried, recrystallised from suitable solvent. The characterization data are given in TABLE 1

1-[3-(4-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl]-4-phenylazetidin-2-one. (Microwave method) (5a-e)

The Schiff's base (0.002 mole, 0.5g) in DMF (10 ml) was taken in beaker to this acetyl chloride (0.002 mole, 0.056g) and triethyl amine (0.002 mole) 0.156 gm were added and it was irradiated in a microwave oven inside MC767W (Electrolux) 4-5 min. Progress of reaction was monitored by TLC. After complication of the reaction, the contents were poured into crushed ice. The solid obtained was filtered off, washed with water and purified by recrystalisation from ethanol to get Schiff base (4a-e). The characterization data are given in TABLE 1

RESULT AND DISCUSSION

The compounds synthesized during the present investigation were established on the basis of analytical, physical and spectral data as IR, ^{1}HNMR and mass spectra. 4-amino-5-(4-chlorophenyl)-4H-1,2,4-triazole-3-thiol **(3)** were prepared by the reaction of 4-chlorobenzoic acid and thiocarbohydrazide, The solid obtained in good yield.

The compound **(3)** displayed the characteristic absorption bands in its IR spectrum 3344 cm^{-1} due to NH_2, 2954 cm^{-1} due to C-H stretching of aromatic, 1530 cm^{-1} due to C=N, 1157 cm^{-1} due to C-S and 744 cm^{-1} due to C-Cl functional groups. The ^{1}HNMR spectrum of compound **(3)** exhibited signal at δ 4.0 (s, 2H, NH_2), δ 7.2-8.1(m, 4H, Ar-H) and δ 9.3 (s, 1H, SH). Further structure of compound is supported by its mass spectrum exhibited a molecular ion peak at m/z, 226 (m^+) and 228 (m^{+2}) its isotopic peak. The other predominant peaks are obtained at m/z 221, 205, 102, 59, 43. When a mixture of 4-amino-5-(4-chlorophenyl)-4H-1, 2, 4-triazole-3-thiol with benzal- dehyde and anhydrous zinc chloride were irradiated inside a MC 767 W (Electrolux) for 2-3 min. The product obtained in good yield.

The compound **(4a)** displayed the characteristic absorption bands in its IR spectrum 3450 cm^{-1} C-H stretching of aromatic, 2921 cm^{-1} due to C-H Stretching, 2854 cm^{-1} due to N = CH Stretching, 1174 cm^{-1} due to C-S and 745 cm^{-1} due to C-Cl functional groups. The ^{1}HNMR spectrum of compound **(4a)** exhibited signal at δ 7.2-8.2 (m, 9H, Ar-H), 9.3 (s, 1H, SH) and δ 9.9 (s, 1H, N=CH). Further the structure of compound **(4a)** is supported by mass spectrum exhibited a molecular

ion peak at m/z, 314 (m^+) and 316 (m^{+2}) its isotopic peak. The other predominant peaks are obtained at m/z 299, 282, 236, 211, 154, and 102.

The mixture of 4-(benzylideneamino)-5-(4-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol, acetyl chloride, triethylamine were taken and irradiated inside a MC 767 W (Electrolux) for 4 min, The product obtained in good yield.

The compound **(5a)** displayed the characteristic absorption bands in its IR spectrum 2921 cm^{-1} C-H stretching of CH_2, 1722 cm^{-1} due to C=O, 1458-1319 cm^{-1} due to C =C, 1088 cm^{-1} due to C-S and 745 cm^{-1} due to C-Cl functional groups. The ^{1}HNMR spectrum of compound **(5a)** exhibited signal at δ 3.4-3.6 (d, 2H, CH_2 of azetidine), δ 4.5 - 4.8 (t, 1H of CH-Ph), δ 6.6 - 7.6 (m, 9H, Ar-H) and δ 9.6 (s, 1H, SH).

Further structure of compound **(5a)** is supported by mass spectrum exhibited a molecular ion peak at m/z, 356 (m^+) and 358 (m^{+2}) its isotopic peak. The other predominant peaks are obtained at m/z 313, 293, 266, 251, 174, and 118 thus the spectral data's were in agreement with its structure.

Antibacterial and antifungal activity

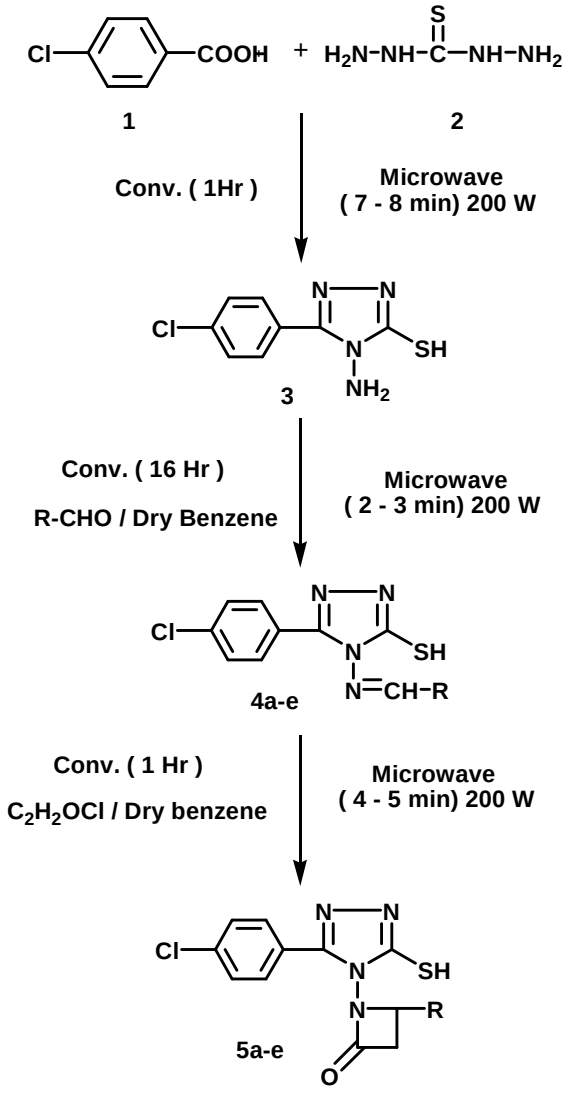
The newly synthesized compounds were subjected to *invitro* antimicrobial activity against by Cup-Plate diffusion method[8] using organisms *E.coli, P.aeruginosa, S.epiermatitis, B.subtilis* for antibacterial activity where as *A.niger* and *C.albican* for antifungal activity. All the test compounds were prepared at the concentration of 100µg/ml in distilled DMF. The standard solution of ciprofloxacine and flucanazole were prepared at the concentration of 100µg/ml in sterile water for compression of antibacterial and antifungal activities and DMF was used as control for both activity, the results were presented in TABLE 2.

The compounds **(3)**, **(4b)**, **(4d)**, **(4e)**, **(5a)**, **(5b)** and **(5c)** shown good antibacterial activity against *E.coli, P.aeruginosa, S.epiermatitis,B.subtilis* and remaining compounds are exhibited moderate activity against the *E.coli, P.aeruginosa, S.epiermatitis,B.subtilis.* In fungicidal activity the compounds **(3)**, **(4b)**, **(4d)**, **(4e)**, **(5a)**, **(5c)** and **(5e)** exhibited significant antifungal activity against *A.niger* and *C.albican* where as remaining compounds are exhibited moderate to weak activity against the *A.niger* and *C.albican,* The results were presented in TABLE 2.

TABLE 2 : Antimicrobial activity of synthesized compounds

Comp No	Zone of inhibition in mm*					
	Antibacterial activity				Antifungal activity	
	E.coli	*P.aeruginosa*	*S.epiermatitis*	*B.subtilis*	*A.niger*	*C.albicans*
3	16	17	15	13	18	16
4a	12	15	16	16	16	16
4b	16	12	16	10	17	17
4c	16	16	12	11	10	16
4d	12	11	10	10	17	18
4e	16	17	14	13	18	16
5a	16	17	15	14	18	17
5b	19	18	17	16	16	10
5c	16	18	15	14	17	18
5d	08	06	07	10	11	17
5e	14	15	14	15	17	18
Ciprofloxacin (Std)	16	17	17	18	--	--
Fluconazole (Std)	--	--	--	--	22	20
Control	6	6	6	6	6	6

***Zone of inhibition in mm**



Scheme I

where R = a)C_6H_5, b)C_6H_4Cl(p), c)C_6H_4OH(p), d)C_6H_4Br(p), e)$C_6H_4N(CH_3)_2$

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