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Synthesis and antimicrobial screening of some novel (E)-4-(arylideneamino)-N-(4-bromophenyl)-5-mercapto-4H-1,2,4-triazole-3-carboxamide derivatives

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ABSTRACT

A convenient synthesis of substituted 1,2,4-triazole-3-carboxamide was carried out by cyclization of potassium dithiocarbazinate with hydrazine hydrate. The compound which has been synthesized was further condensed with various substituted aromatic aldehyde to get target compound (E)-4-(arylideneamino)-n-(4-bromophenyl)-5-mercapto-4h-1,2,4-triazole-3-carboxamide (Schiff's base). The newly synthesized compound were characterized by ^{1}H NMR,^{13}C NMR, IR, MS, elemental analysis and screened for their antimicrobial activity against various strains of bacteria and fungi.

KEYWORDS

1,2,4-triazole-3-carboxamide;
Schiff's base;
Antibacterial activity;
Antifungal activity.

INTRODUCTION

Triazoles are heterocyclic organic compounds having a five-member ring molecular structure containing three nitrogen atoms. Triazoles are of two types: 1, 2, 4- triazole and 1, 2, 3-triazole.1,2,4-triazole and their derivatives constitute an important class of organic compounds which exhibits diverse pharmacological, agricultural and industrial profile[1-3] such as antimicrobial[4-5], anti-convulsant[6-7] and anti-inflammatory[8]. The first 1, 2, 4-triazole derivative was synthesized by Bladin in 1885. Synthesis of various triazole derivatives have been reported[9-15]. Alkinson and Polya[16] synthesized 1,3-diphenyl 1,2,4, triazole. From diaroylhydrazines, Klingsberg[17] prepared triaryl-s-triazoles. Kurzer and Canelle[18] synthesized some 4-substitutetd 3-amino-5- mercapto-1,2,4-triazoles. Beresneva et al.[19] reported synthesis of 3-(1,2,4-trazole-4- yl)-5-amino 1,2,4-triazole. Preparation and characterization of four isomeric oxodihydro s-triazolo pyrimidines was studied by Reimlinger and Peiren[20]. Synthesis of various new triazoles have also been reported by several workers[21-23].

Chemistry and pharmacological activity of such substituted triazole compounds prompts us to synthesize a series of new potentially active groupbearing the 1, 2, 4-triazole nucleus. Prompted by these observations, it was contemplated to synthesize some 1, 2,4-triazole-3-carboxamide derivatives containing Schiff base with the view to explore their potency as better pharmaceutical agent.

EXPERIMENTAL

Thin-layer chromatography was accomplished

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on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H (400 MHz), ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in $CDCl_3$ and DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.

General procedure for the synthesis N-(4-bromophenyl)-2-hydrazinyl-2-oxoacetamide (Int 1)

To the 1 N RBF 4-bromo aniline (0.09 mol) and diethyl oxalate (0.09 mol) in toluene (100 ml) was refluxed for 8-12h. The progress of the reaction was monitored on TLC by using mobile phase Ethylacetate:Hexane (1:9). After completion of reaction the reaction mixture poured in chilled dilute HCl solution to remove the unreacted aniline. The separated layer of toluene containing desired ester was separated and the water layer extracted two times with Ethyl acetate. The Combined Solvent layer was dried with Na2SO4 and distilled out to get ester as a white solid. This white solid was dissolved in methanol and treated with Hydrazine hydrate (0.135 mol). The white solid suddenly fall out was filtered and wash with methanol to give 9 g hydrazide intermediate. Yield:66%

General procedure for the synthesis of (E)-4-(arylideneamino)-N-(4-bromophenyl)-5-mercapto-4H-1,2,4-triazole-3-carboxamide (Int-2)

To a mixture of potassium hydroxide (0.045 mol) and N-(4-bromophenyl)-2-hydrazinyl-2-oxoacetamide (0.045 mol) in methanol, carbon disulphide (0.068 mol) was added. This mixture was stirred for 12 h. Excess methanol was distilled under reduced pressure on rotary evaporator. The residue was refluxed with excess 80% hydrazine hydrate for 3h. The color of the reaction mixture changed to green, hydrogen sulfide was evolved and a homogeneous solution resulted. Dilute the solution with cold water and neutralized with glacial acetic acid, precipitated a white solid. The product was filtered, washed with cold water. On drying 5 g white solid obtained. yield :25%

General procedure for the synthesis of (E)-4-(arylideneamino)-N-(4-bromophenyl)-5-mercapto-4H-1,2,4-triazole-3-carboxamide (Compound 1a-1t)

Equimolar amount of triazole and appropriate aldehyde were taken in methanol and added 2 drops of con. HCl as a catalyst. The reaction mixture was

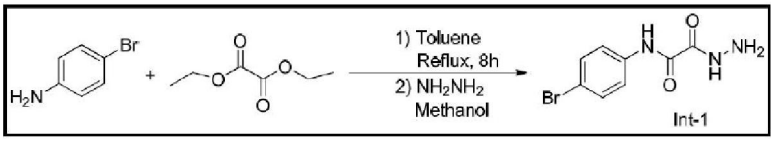

Figure 1: Reaction Scheme for N-(4-bromophenyl)-2-hydrazinyl-2-oxoacetamide

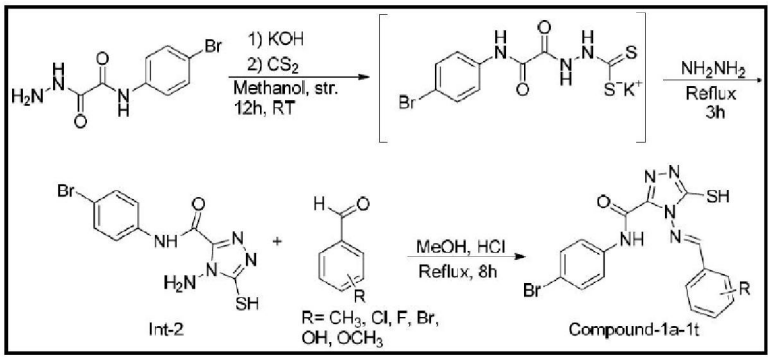

Figure 2: Reaction Scheme for Compound-1a-1t

TABLE: 1 Physical data of synthesized compound

Entry	R	Time h	Yield %	Melting Range ^{0}C
1a	-H	7	81	162-164
1b	-4-Cl	8	74	192-194
1c	-4-F	8	79	187-189
1d	-4(N, N-dimethylamino)	9	82	172-174
1e	-4-Me	6	65	188-190
1f	-3-F	6	91	180-182
1g	-2-Cl	8	71	184-186
1h	-2,4-di Cl	8	59	188-190
1i	-3,4-di OMe	7	87	196-198
1j	-4-OMe	8	78	178-180
1k	-2-OH	6	67	182-184
1l	-3-OH	7	73	176-178
1m	-2,5-di OMe	8	79	190-192
1n	-3-Cl	8	83	188-190
1o	-3-Br	8	85	176-178
1p	-4-OH	7	72	188-190
1q	-2-NO_2	9	66	184-186
1r	-3-NO_2	9	69	196-198
1s	Cinnamaldehyde	8	77	168-170
1t	Naphthaldehyde	8	82	180-182

refluxed for 8 h. and allowed to cool at room temperature. The solid was filtered, dried and recrystallized from ethanol to give pure yellow crystals in 85-90% yield.

(E)-N-(4-bromophenyl)-4-((3-fluorobenzylidene) amino)-5-mercapto-4H-1,2,4-triazole-3-carboxamide (Compound-1f)

yellow solid; Melting range:180-182°C; R_f 0.47 (6:4 hexane-EtOAc); IR (KBr): 3284, 3186, 3055, 2916, 1691, 1618, 1577, 1508, 1464, 1384, 1261, 1165, 1101, 1051, 954, 866, 839, 788, 646, 518 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): *δppm*7.238-7.255(d, *J*=6.8 Hz 2H, Ar-H), 7.730 (t, 1H, Ar-H), 7.742-7.759(d, *J*=6.8 Hz, 2H, Ar-H), 7.849-7.869(d, *J*=8 Hz, 2H, Ar-H), 9.429 (s, 1H, -N=CH-), 11.079(s, 1H, -NH-), 14.654(s, 1H, -C-SH); MS (*m/z*):420 (M^+); Anal. Calcd for $C_{16}H_{11}BrFN_5OS$: C, 45.73; H, 2.64; N, 16.66; Found: C, 46.81; H, 2.95; N, 21.47.

(E)-N-(4-bromophenyl)-5-mercapto-4-((4-methoxybenzylidene)amino)-4H-1,2,4-triazole-3-carboxamide (Compound-1j)

yellow solid; Melting range:178-180°C; R_f 0.49 (6:4 hexane-EtOAc); IR (KBr): 3553, 3238, 2993, 2306, 1905, 1683, 1599, 1543, 1481, 1367, 1265, 1170, 974, 891, 802, 773, 668, 619 cm^{-1};^{1}H NMR (400 MHz, DMSO): *δppm*3.857(s, 3H, -OCH_3), 7.107 -7.129(d, *J*=8.8 Hz, 2H, -Ar-H), 7.209-7.231(d, *J*=8.8 Hz, 2H, Ar-H), 7.806-7.828(d, *J*=8.8 Hz, 2H, Ar-H), 7.868-7.889(d, *J*=8.4 Hz, 2H, Ar-H), 9.197(s, 1H, -N=CH-), 11.022(s, 1H, -NH), 14.544(s, 1H, -C-SH);MS (*m/z*):432 (M^+); Anal. Calcd for $C_{17}H_{14}BrN_5O_2S$: C, 47.23; H, 3.26; N, 16.20; Found: C, 45.78; H, 4.55; N, 15.75.

RESULT AND DISCUSSION

Various methodologies have been described for the synthesis of 1,2,4-triazolo-3-carboxamide derivatives. During the course of our ongoing interest on synthesis of various heterocyclic compounds usingN-(4-bromophenyl)-2-hydrazinyl-2-oxoacetamide, we observed that N-(4-bromophenyl)-2-hydrazinyl-2-oxoacetamide are versatile intermediate for the synthesis of 1,2,4-triazole-

TABLE 2 : Antimicrobial screening result of compound 1a-1t

Sr.No.	Code no.	MIC (µg/mL)						
		antibacterial activity				antifungal activity		
		E.coli	*P.aeruginosa*	*S.aureus*	*S.pyogenus*	*C.albicans*	*A.niger*	*A.clavatus*
1	1a	500	500	500	500	500	500	>1000
2	1b	250	250	200	250	500	500	250
3	1c	500	500	250	500	500	500	1000
4	1d	100	500	250	500	500	500	>1000
5	1e	500	500	500	500	500	500	500
6	1f	500	100	100	250	200	250	250
7	1g	500	200	250	500	500	1000	500
8	1h	250	250	200	250	250	500	500
9	1i	200	250	500	250	100	100	100
10	1j	200	250	200	500	500	250	500
11	1k	500	250	250	250	200	500	500
12	1l	500	250	250	250	500	1000	500
13	1m	100	200	500	125	500	250	250
14	1n	250	200	500	250	250	250	500
15	1o	500	500	250	500	1000	1000	500
16	1p	250	200	500	200	250	250	500
17	1q	250	500	500	200	500	250	250
18	1r	500	250	250	250	250	500	250
19	1s	250	200	250	500	500	500	1000
20	1t	500	500	250	500	500	500	500
Gentamycin		0.05	1	0.25	0.5	-	-	-
Ampicilin		100	100	250	100	-	-	-
Chloramphenicol		50	50	50	50	-	-	-
Ciprofloxacin		25	25	50	50	-	-	-
Norfloxacin		10	10	10	10	-	-	-
Nystatin		-	-	-	-	100	100	100
Greseofulvin		-	-	-	-	500	100	100

3-carboxamide. Thus, to synthesized target molecules, the various N-(4-bromophenyl)-2-hydrazinyl-2-oxoacetamide (Int-1) were reacted with various substituted aldehyde in the presence hydrochloric acid as catalyst and methanol as solvent at reflux temperature to afford 1,2,4-triazolo-3-carboxamide derivatives (Compound-1a-1t) (TABLE 1). All the synthesized compounds were screened against varieties of bacterial strains and fungi (TABLE 2) such *E.coli, S.pyogenus, S.aureus, P.aeruginosa, C.albicans, A.niger, A.clavatus* at minimal inhibitory concentration (MIC). Standard drugs like Ampicillin, Chloramphenicol, Nystatin, Gentamycin, Ciprofloxacin, and Greseofulvin were used for the comparison purpose.

CONCLUSION

In summary, A series of novel 1,2,4-triazole derivatives were synthesized in appreciable yields and characterized by NMR, mass spectrometry and IR studies. The newly synthesized compounds were screened for antibacterial and antifungal activity. The reaction of N-(4-bromophenyl)-2-hydrazinyl-2-oxoacetamide with hydrazine hydrate and followed by condensation with various aromatic aldehyde to afford targeted compound in moderate to good yield in the presence of acid. All the synthesized com-

pounds were evaluated for their antimicrobial activity. The investigation of antimicrobial and antifungal screening data revealed that all the tested compounds showed moderate to significant activity.

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