Asian Journal of Chemistry Vol. 21, No. 6 (2009), 4733-4736

Synthesis and Biological Evaluation of 5-Pyridine-4-(arylidine amino)-3-mercapto-4(*H*)-1,2,4-triazoles

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As triazoles have proven to be good antimicrobial agents, a new series of triazole derivatives were synthesized and characterized by ^{1}H NMR, IR, GCMS sophisticated analytical instruments and were evaluated for their antimicrobial activity. Out of several derivatives synthesized a few of 5-pyridine-4-(arylidine amino)-3-mercapto-4(*H*)-1,2,4-triazoles showed good antimicrobial activity by using cup-plate method.

Key Words: Arylidine derivatives, 1,2,4-Triazole, Antimicrobial activity.

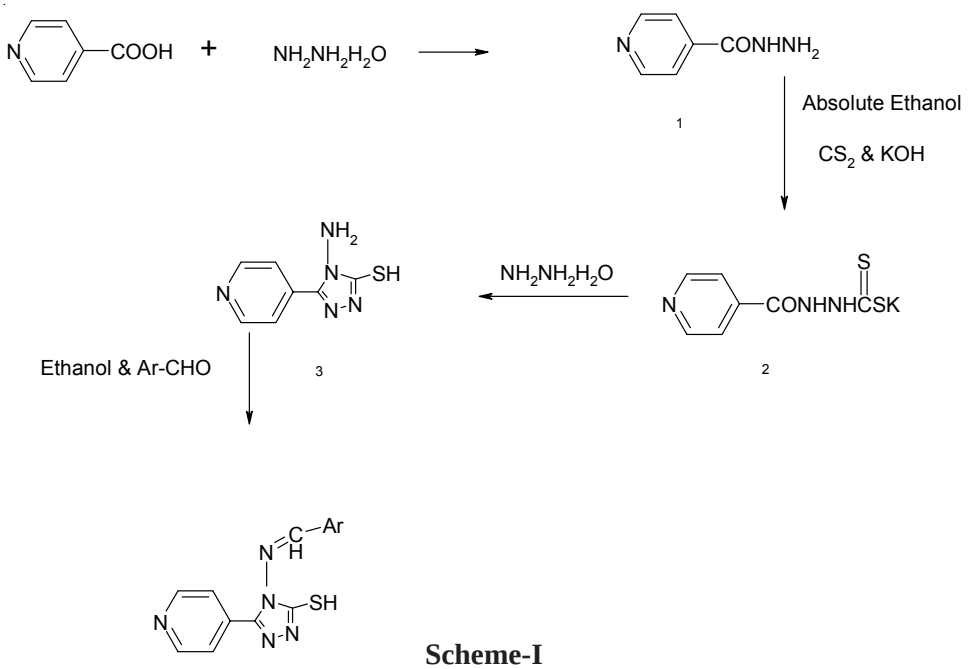
INTRODUCTION

Microbial infections are most common infections and commonly used antibacterials, antifungals are antibiotics and recently used halogenated quinolones, azoles and other synthetic agents are being used to combat the newer and resistant microbial infections. Azoles in particular 1,2,4-triazoles have shown significant antimicrobial activity[1-6]. Compounds with the azomethine linkage possess biological activity such as antifungal[7], antibacterial[8] and antiinflammatory[9] activity. Herein, an attempt is made to synthesize Schiff bases of 5-pyridine-4-(arylidine amino)-3-mercapto-4(*H*)-1,2,4-triazoles as potent antimicrobial agents.

EXPERIMENTAL

All chemicals were used after purification and supplied by Loba Chemie, Qualigens and Research Labs. Melting points of newly synthesized compounds were determined in open capillary tube and were found uncorrected. The structure of the synthesized compounds was confirmed by spectral data. The IR spectra were recorded on FTIR 8400 F-Shimadzu spectrometer using KBr disc pellet method. ^{1}H NMR spectra were recorded on Verian mercury ^{1}H 300 using DMSO as solvent. GCMass spectra were recorded on GCMS-QP-5050 Schimadzu.

Synthesis of isonicotinyl hydrazide (1): In round bottom flask, 4-pyridine carboxylic acid (0.01 mol) and hydrazine hydrate 99 % (0.01 mol) was taken along with alcohol and the mixture was refluxed for 4 h. Then from the reaction mixture alcohol was removed under reduced pressure. Solid residue was obtained, recrystallized with ethanol.



Scheme-I

Synthesis of potassium-pyridine-dithiocarbazate (2): In a 250 mL round bottom flask, aryl hydrazide 10.28 g (0.075 mol) was taken. To this a solution of potassium hydroxide 4.2 g (0.075 mol) in 100 mL of absolute alcohol and carbon disulphide were added agitated for overnight. The reaction mixture was diluted with 200 mL of dry ether. The solid obtained was 15.05 g (80 %). It was filtered and washed with dry ether.

Synthesis of 5-pyridine-4-amino-3-mercapto-4(*H*)-1,2,4-triazole (3): A mixture of potassium-pyridine-dithiocarbazate 25.1 g (0.1 mol) and hydrazine hydrate 5 mL (0.1 mol) was refluxed for 2 h with occasional shaking and the solution was poured into the cold water. The mixture was acidified with hydrochloric acid. The precipitate obtained was filtered, dried and recrystallized by using alcohol. IR (KBr, ν_{max}, cm^{-1}): 3309 (w, NH_2, *str.*), 2677 (w, SH, *str.*), 2358 (s, CH_2, *str.*). ^{1}H NMR (DMSO-d_6): 1.5 (s, 1 H, SH), 5.38 (s, 2H, CH_2).

Synthesis of 5-pyridine-4-(arylidine amino)-4-mercapto-4(*H*)-1,2,4-triazoles (4): A mixture of 5-pyridine-4-amino-3-mercapto-4(*H*)-1,2,4-triazole (0.01 mol) taken with various aromatic aldehydes (0.01 mol) and concentrated sulphuric acid (0.5 mL) in ethanol 100 mL. The mixture was refluxed on water bath for several hours with TLC monitoring. The solid was obtained on cooling the mixture and poured in cold water was afforded the Schiff's bases (**4a-4m**) (Table-1). IR (KBr, ν_{max}, cm^{-1}): 2677 (w, SH, *str.*), 2358 (s, CH_2, *str.*), 1596 (w, C=N, *str.*). ^{1}H NMR (DMSO-d_6): 14 (s, 1 H, SH), 5.38 (s, 2H, CH_2), 9.43 (w, 1H, OH), 3.0 (s, 6H, $2CH_3$), 10.0 (w, 1H, N=CH). Mass: (i) 271 (M^+-1), 44 (Base peak), 57, 71, 78, 91, 105, 119, 178.

TABLE-1
PHYSICAL DATA OF SOME 5-PYRIDINE-4-(ARYLIDINE AMINO)-4-MERCAPTO-4(*H*)-1,2,4-TRIAZOLES
Recrystallization solvent: Ethanol

Compd.	Ar	m.f.	m.w.	m.p. (ºC)	Yield (%)
4a	Furan	$C_{12}H_9N_5OS$	271	290	45
4b	*o*-Cl-Phenyl	$C_{14}H_{10}N_5SCl$	315	304	48
4c	*p*-OH-Phenyl	$C_{14}H_{11}N_5OS$	297	272	60
4d	*p*-OCH_3-Phenyl	$C_{15}H_{13}N_5OS$	311	290	45
4e	*p*-Cl-Phenyl	$C_{14}H_{10}N_5SCl$	315	225	50
4f	*p*-N-Dimethyl-phenyl	$C_{16}H_{16}N_6S$	324	211	50
4g	Phenyl	$C_{14}H_{11}N_5S$	281	242	45
4h	*p*-OH-M-Methoxy-phenyl	$C_{15}H_{13}N_5O_2S$	327	270	50
4i	*p*-Nitro-phenyl	$C_{14}H_{10}N_6O_2S$	326	275	50
4j	*o*-Nitro-phenyl	$C_{14}H_{10}N_6O_2S$	326	230	50
4k	*m*-Hydroxy-phenyl	$C_{14}H_{11}N_5OS$	297	246	55
4l	*m*-Nitro-phenyl	$C_{14}H_{10}N_6O_2S$	326	290	45
4m	*o*-OH-phenyl	$C_{14}H_{11}N_5OS$	297	208	60
3	Triazole	$C_8H_6N_5S$	204	260	60

TABLE-2
ANTIMICROBIAL ACTIVITY OF SOME 5-PYRIDINE-4-(ARYLIDINE AMINO)-4-MERCAPTO-4(*H*)-1,2,4-TRIAZOLES

Compd.	Zone of inhibition (mm)											
	B. subtillis		*S. aureus*		*K. pneumoniae*		*P. aeruginosa*		*C. albicans*		*A. niger*	
Conc.[n]	A	B	A	B	A	B	A	B	A	B	A	B
4a	2	5	3	6	3	5	3	5	4	8	5	9
4b	2	4	6	8	4	9	5	7	6	10	5	9
4c	4	9	5	7	6	8	5	8	4	6	3	7
4d	5	7	3	5	5	8	4	9	4	5	3	8
4e	2	5	4	8	6	9	4	6	5	10	4	9
4f	5	8	6	9	3	5	4	6	4	9	5	9
4g	3	7	3	5	5	9	6	7	8	11	10	12
4h	4	8	5	9	6	10	5	9	8	13	9	13
4i	5	8	7	9	6	10	7	10	3	7	5	8
4j	6	9	8	12	4	7	3	9	4	6	6	10
4k	3	8	4	6	7	13	4	9	5	9	6	8
4l	3	5	2	7	5	7	5	9	3	8	4	10
4m	4	9	3	8	6	10	3	8	5	10	6	11
3	6	8	4	7	6	8	4	6	6	10	7	11
Norfloxacin 50 µg/0.1 mL					14 mm							
Griseofulvin 50 µg/0.1 m					13 mm							

A = 200 µg/0.1 mL; B = 400 µg/0.1 mL. All tests were performed in triplicate.

Antimicrobial activity: The antimicrobial activity was carried out by using cup-plate method[10,11] by using microbial strains as *Bacillus subtillis, Staphylococcus aureus, Pseudomonas aerugenosa* and *Kleibsella pneumonia* with incubation

period of 24 h at temperature 37 ºC. The standard drug used was norfloxacin (50 µg/0.1 mL) and the test compounds at concentrations of 200 and 400 µg/0.1 mL.

Antifungal activity was carried out using cup-plate method[10,11]. By using fungal strains as *Aspergillus niger, Candida albicans*, for 48 h of incubation at 28 ºC. The concentration of the standard drug griseofulvin was used 50 µg/0.1 mL and the test compounds at concentrations of 200 and 400 µg/0.1 mL (Table-2).

RESULTS AND DISCUSSION

All the compounds tested showed some degree of antimicrobial activity **4h**, **4i**, **4j**, **4k** and **4m** showed good antibacterial activity and **4g**, **4h**, **4i**, **4j**, **4k**, **4l**, **4m** and **3** showed good antifungal activity due to presence of triazole nucleus in it. Due to presence of imino group and shifted SH group in compounds ^{1}H NMR spectra indicate completion of target reactions in this series.

ACKNOWLEDGEMENTS

The authors dedicated this paper and thanks Prof. M.Y. Yedukondalu, Principal, College of Pharmacy, Mohuda, for his kind help, support and encouragement.

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(*Received*: 11 September 2008; *Accepted*: 31 March 2009) AJC-7387