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Synthesis, characterization and antibacterial activity studies of some triazolothiadiazolylquinolines

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ABSTRACT

Cinchonic acids are the useful synthons for the preparation of quinoline derivatives. They were prepared by employing Pfitzinger reaction starting from isatins and 2-acetylfuran. 3-Aryloxymethyl-4-amino-5-mercapto-1,2,4-triazoles on reacting with cinchonic acids in the presence of phosphorus oxychloride yielded 2-(2-furyl)-4-(3-aryloxymethyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-6-yl)quinolines. The structures of these compounds were confirmed on the basis of elemental analysis and spectral data. These compounds were screened for their antibacterial activities against gram-positive and gram-negative bacteria.

Keywords: 1,2,4-Triazoles, quinolines, synthesis, characterization, antibacterial activity.

INTRODUCTION

1,2,4-Triazoles are associated with diverse pharmacological activities. The analgesic, antibacterial, antifungal, anti-inflammatory, antiviral etc., properties exhibited by various 1,2,4-triazoles have made them as important chemotherapeutic agents[1-7]. Quinoline derivatives are also associated with various pharmacological properties such as antimalarial, antimicrobial, antiviral, antipyretic etc[8-13]. Quinoline ring fused with a heterocyclic system is found in many natural products.

In this paper, the results of studies on the reactions of 3-aryloxymethyl-4-amino-5-mercapto-1,2,4-triazoles with cinchonic acids and their antibacterial properties are reported.

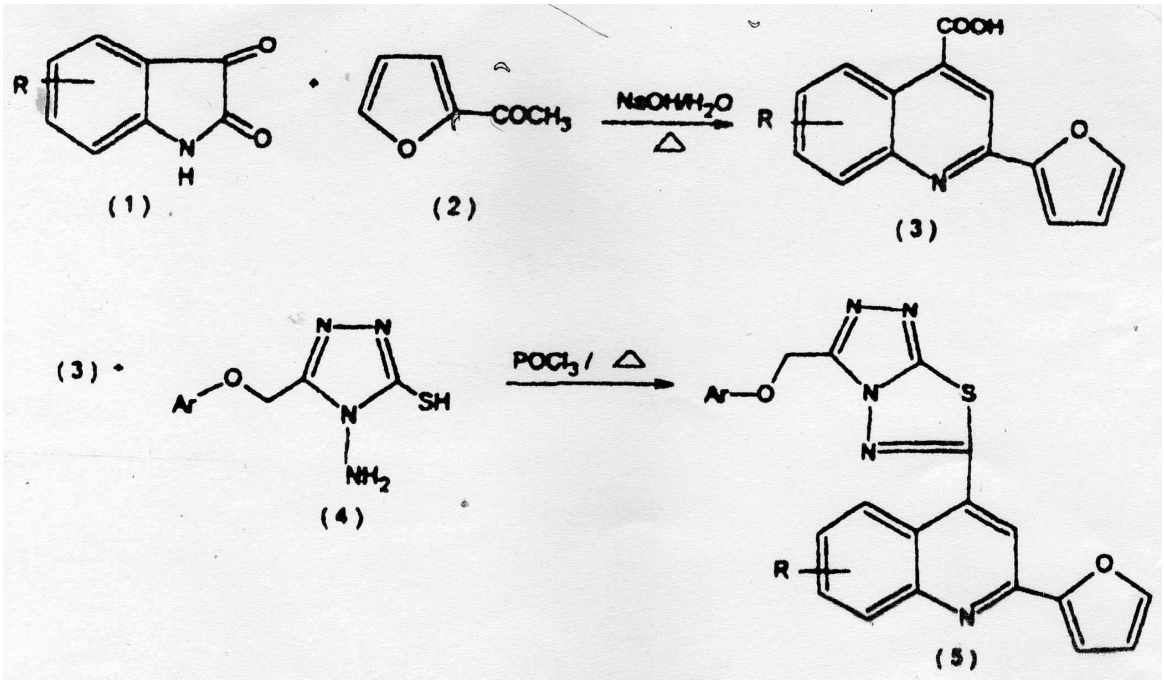
EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (cm^{-1}) were recorded in KBr pellets on a Shimadzu IR Spectrophotometer and NMR spectra on a Perkin Elmer R 32 spectrometer using $CDCl_3$ as a solvent. Standard chemical shift values are given in δ ppm. Mass spectra were recorded on a Jeol JMS-D 300 mass spectrometer operating at 70 eV. Compounds were checked for their purity by TLC on silica gel plates and spots were visualized in iodine vapour.

Synthesis of Cinchoninic acids 3

A solution of sodium hydroxide(2g, 0.05 mol) and appropriate isatin(0.01 mol) in water (25 ml) was heated on a water bath for 45 min. A clear solution was obtained. 2-Acetylfuran(1.1 g, 0.01 mol) was added to it in small proportions with occasional shaking. Heating was continued for 2.5 hr. The reaction mixture was chilled in ice bath. The solid mass of the sodium salt of cinchoninic acid was collected by filtration through a sintered glass crucible(G-4). The residue was dissolved in water and acidified with glacial acetic acid. Compounds prepared employing this procedure are:

a. 2-(2-furyl)cinchoninic acid, yield 72%, m.p. 226 ^{0}C(lit.[14] m.p. 227 ^{0}C).
b. 2-(2-furyl)-6-methylcinchoninic acid, yield 62%, m.p. 254 ^{0}C(lit.[11] m.p. 254-255 ^{0}C).
c. 2-(2-furyl)-6-bromocinchoninic acid, yield 68%, m.p. 282^{0}C.



Scheme 1

Synthesis of 2-(2-furyl)-4-(3-aryloxy methyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-6-yl) quinolines 5a-k

A mixture of 3-aryloxymethyl-4-amino-5-mercapto-1,2,4-triazole (0.01mol), 2-(2-furyl)cinchoninic acid (0.01 mol) and phosphorus oxychloride(10 ml) was heated on a water bath for 2 hr. The reaction mixture was cooled to room temperature and poured onto crushed ice. The solid mass so obtained was collected by filtration and washed with sodium bicarbonate (5%) solution and then with excess of water. It was recrystallized from a mixture of ethanol and dimethylformamide(2:1). The characterization data of these compounds are given in Table 1.

The physical characterization data of all the compounds has been summarized in Table 1.

Table 1-Physical characterization data of compounds (5)

Compd	R	Ar	Yield (%)	M.P. (^{0}C)	Mol formula	Elemental Analysis Found(Calcd.)		
						%C	%H	%N
5a	Br	p-ClC_6H_4	63	222	$C_{23}H_{13}BrClN_5O_2S$	51.58 (51.26)	2.33 (2.41)	12.91 (13.0)
5b	Br	o-ClC_6H_4	68	184	$C_{23}H_{13}BrClN_5O_2S$	51.08 (51.26)	2.32 (2.41)	12.77 (13.0)
5c	Br	p-MeC_6H_4	67	171	$C_{24}H_{16}BrN_5O_2S$	55.24 (55.61)	2.91 (3.09)	13.33 (13.51)
5d	Br	o-MeC_6H_4	61	210	$C_{24}H_{16}ClN_5O_2S$	55.52 (55.61)	2.97 (3.09)	13.74 (13.51)
5e	Me	p-ClC_6H_4	68	182	$C_{24}H_{16}ClN_5O_2S$	60.48 (60.82)	3.24 (3.38)	14.60 (14.78)
5f	Me	o-ClC_6H_4	72	212	$C_{24}H_{16}ClN_5O_2S$	60.47 (60.82)	3.06 (3.38)	14.41 (14.78)
5g	Me	p-MeC_6H_4	64	191	$C_{25}H_{19}ClN_5O_2S$	66.08 (66.23)	4.11 (4.19)	15.16 (15.45)
5h	Me	o-MeC_6H_4	70	198	$C_{25}H_{19}ClN_5O_2S$	66.56 (66.23)	3.97 (4.19)	15.32 (15.45)
5i	H	p-ClC_6H_4	71	182	$C_{23}H_{14}ClN_5O_2S$	60.22 (60.0)	3.22 (3.05)	15.64 (15.23)
5j	H	p-MeC_6H_4	68	170	$C_{24}H_{17}ClN_5O_2S$	65.31 (65.60)	3.52 (3.87)	15.71 (15.95)
5k	H	o-MeC_6H_4	65	178	$C_{24}H_{17}ClN_5O_2S$	65.49 (65.60)	3.76 (3.87)	15.90 (15.95)

Antibacterial activity studies:

Antibacterial activity of some of the selected compounds were studied against *P.aeruginosa*, *E.coli*, *P. vulgaris*, *S.typhi* and *S.aureus* according to disc-diffusion method[16]. The antibacterial activity was determined by measuring the diameter of the zone of inhibition. Nitrofurazone, the well-known topical antibacterial agent was used as a standard drug for comparison and the solvent control was kept. Most of the compounds did not exhibit any significant antibacterial activity. Compound **5i** possessing a chlorophenoxy substituent at C-3 of the triazole ring was active against both Gram-positive and Gram-negative bacteria. The screening data are given in Table 2.

The antibacterial activity of the test compounds were also determined against *S.aureus, P.aeruginosa, E.coli and B.subtilis* by serial dilution method. The test compound was dissolved in dimethylformamide (5 ml) to prepare a stock solution of concentration 1000 ug/ml. One loopful of an 18 hour broth culture was inoculated into 5 ml of nutrient broth and this was incubated at 37 0C for 4 hours. An assay was prepared by diluting 4 hour subculture in 1/1000 in nutrient broth. Nutrient broth (0.5 ml) was taken in tubes with labeled numbers 1-11. An aliquot 0.5 ml of stock solution of test compounds was added to the first tube. The solution was mixed well and 0.5 ml of this solution was transferred into second tube. This process was repeated serially to obtain the quantities indicated in each of the test tubes. The eleventh tube was taken as growth control. Drops of diluted broth culture of the test organism(approximately 0.05 ml) was added into all the tubes using a sterilized Pasteur pipette. The solutions were mixed gently and the incubation was carried out at 37 ^{0}C for 16-18 hours. Furacin dissolved in dimethylformamide was used as standard drug for comparison. The minimum concentration at which there was no turbidity was taken as minimum inhibitory concentration (MIC) and the results are tabulated in Table 3.

Table 2-Antibacterial activity of triazolothiadiazolylquinolines(5)

Compd	Zone of inhibition (in mm)				
	P.aer	*E.coli*	*P.vul*	*S.typhi*	*S.aureus*
5a	--	--	13.0	--	trace
5b	--	--	--	trace	7.8
5e	--	7.3	8.4	8.6	--
5f	--	trace	7.15	8.5	8.4
5h	trace	--	trace	10.0	--
5i	7.95	7.7	8.6	8.25	9.0
Nitrofurazone	--	10.8	10.2	14.7	14.25

Table 3- Antibacterial activity data of triazolothiadiazolylquinolines(5)

Compd No.	Minimum Inhibitory Concentrations(MIC)			
	E.coli	*S.aureus*	*P.aeruginosa*	*B.subtilis*
5a	6	6	12.5	12.5
5b	6	6	6	12.5
5c	12.5	12.5	12.5	6
5d	6	12.5	12.5	12.5
5e	12.5	6	12.5	6
5f	12.5	25	12.5	12.5
5g	12.5	12.5	25	25
5h	12.5	12.5	12.5	6
5i	12.5	12.5	12.5	12.5
5j	6	3	12.5	12.5
5k	12.5	12.5	12.5	12.5

RESULTS AND DISCUSSION

Substituted isatins were prepared starting from anilines per the lieterature metod[15]. These compounds were subjected to Pfitzinger reaction in the presence of 2-acetylfuran to yield cinchoninic acids. Triazoles were made to react with cinchoninic acids in the presence of phosphorus oxychloride. This resulted in the formation of the compounds **5**. The newly

synthesized compounds were characterized on the basis of analytical and spectral data. The IR spectrum of compound **5i** showed absorption peak at 1600 cm^{-1} corresponding to C=N stretching frequency. The C-H deformation of the p-substituted benzene ring was seen at 825 cm^{-1}. The NH_2 str. vibration of the triazole substituent and the OH and C=O str. vibrations of the carboxylic acid group of the cinchoninic acid moiety were not observed in the IR spectrum of **5i** which showed the involvement of these groups in the reaction.

The NMR spectrum of the compound **5a** showed a sharp singlet at δ, 5.66 characteristic of the OCH_2 group of the aryloxymethyl moiety. The furyl 4-H proton of the mono substituted furan ring was observed as a closely spaced doublet at δ, 6.6, while the aromatic protons signal along with the two remaining furyl protons appeared as multiplets in the region δ, 6.9-8.6. Similarly, the NMR spectral data of the following compounds are assigned as follows.

5c: δ, 2.25(s, 3H, CH_3), 5.6(s,2H,OCH_2), 6.6(d,d,1H,furan-4H), 7.1-8.1(m,10H, aryl and furan).
5f: δ, 2.6(s, 3H, CH_3), 5.7(s,2H,OCH_2), 6.6(d,d,1H,furan-4H), 6.9-8.4(m,10H, aryl and furan).
5e: δ, 2.5(s, 3H, CH_3), 5.6(s,2H,OCH_2), 6.6(d,d,1H,furan-4H), 7.1-8.1(m,10H, aryl and furan).
5i: δ, 5.5(s,2H,OCH_2), 6.65(d,d,1H,furan-4H), 7.0-8.6(m,11H, aryl and furan).

Mass spectrum of compound **5e** showed a peak at m/z 473 corresponding to the molecular formula $C_{24}H_{16}ClN_5O_2S$. Peak at m/z 346 is assigned to the loss of p-chlorophenoxy radical from the molecular ion. Peak at m/z 234 was observed due to the formation of quinolino nitrile during the mass spectral fragmentation. The base peak was observed at m/z 84 which corresponds to the formation of CH_2=C=N=C=S ion which is characteristic of aryloxymethyl triazoles. Similarly, the mass spectrum of **5c** showed a peak at m/z 517 corresponding to the molecular formula $C_{24}H_{16}BrN_5O_2S$ assigned for this compound. The appearance of M+2 peak as intense as the molecular ion peak shows the presence of bromine atom in this molecule.

The newly synthesized compounds **5** were screened for their antibacterial activity against *E.coli, S.aureus, P.aeruginosa* and *B.subtilis*. Furacin was used as a standard drug. Their minimum inhibitory concentrations(MIC) were determined according to serial dilution method. The solutions of test compounds were prepared in dimethylformamide medium. The screening data indicated that all the compounds showed moderate to excellent antibacterial activity compared with the standard drug, Furacin.

CONCLUSION

The present work describes a simple and very convenient procedure for the triazolothiadiazolylquinolines. The pharmacological profile of the synthesized compounds revealed that all the compounds showed moderate to excellent antibacterial activity compared with the standard drug, Furacin and hence deserve further in depth pharmacological investigations.

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