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Original Research Paper

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW SCHIFF'S BASES AND 4-OXOTHIAZOLIDINE DERIVATIVES OF 2-MERCAPTOBENZOXAZOLE

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ABSTRACT

The present investigation was aimed at the synthesis of 2-mercaptobenzoxazole, a series of Schiff's bases 1-[α-(arylidine hydrazino) acetyl]-2-mercaptobenzoxazole 2MB-2a-e and 2-[(aryl)-3-(acetyl amino)-1, 3-thiazolidine-4-ones]-2-mercaptobenzoxazole 2MB-3a have been synthesized from 2-mercaptobenzoxazole and compounds were screened for their antibacterial and antifungal activities by agar diffusion method. The structures of the all synthesized compounds have been determined by their IR, 1H NMR and elemental analysis. All the compounds have showed moderate to promising antibacterial and antifungal activities, against Gram-positive bacterium *Bacillus subtilis* (MTCC 441), *Streptomyces griseus* (MTCC 1540) and Gram-negative bacterium *Escherichia coli* (MTCC 443) and for antifungal activity against *Ashbya gossypii* (MTCC 358) and *Aspergillus niger* (MTCC 282).

Keywords: 2-Mercaptobenzoxazole, Schiff's base, 4-Oxothiazolidine, Antibacterial, Antifungal.

INTRODUCTION

Research Program for the discovery of new antimicrobial drugs for improving the evaluation criteria are under way in many laboratories. In addition, knowledge of specific constituents of the bacterial cell and their biochemical role has advanced considerably in the recent years and may permit a more rational approach to the design of new drug acting on specific targets. Among various heterocycles, containing nitrogen, oxygen and sulphur atoms at symmetrical position, they are core structure of a several biological active compounds.[1-3] 2-Mercaptobenzoxazole derivatives have occupied a prominent due to their versatile biological property.[4-5] Similarly 4-oxothiazolodines are also known to possess various biological activities.[6-9] In view of the above mentioned facts and in continuation of our work on the synthesis and screen the antimicrobial activities of Schiff's bases and 4-oxothiazolodine derivatives of 2-mecaptobenzoxazole. The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in scheme for synthesis. 2-Mercaptobenzoxazole (2MB) when treated with chloroacetyl chloride in the presence of anhydrous potassium carbonate in chloroform gave 1-chloroacetyl-2-mercaptobenzoxazole (2MB-1), which on amination with hydrazine hydrate yielded 1-hydrazinoacetyl-2-mercaptobenzoxazole (2MB-2).Condensation of (2MB-2) with appropriate aromatic aldehydes yielded hydrazones derivatives(2MB-2a-e). Compound 2MB-2a on reaction with thioglycolic

acid underwent dehyrdative annulation yielded 2-[(aryl)-3-(acetyl amino)-1, 3-thiazolidine-4-ones]-2-mercaptobenzoxazole 2MB-3a.

MATERIALS AND METHODS

Reagents, Instrumentation and Measurements

All reagents, solvents and catalyst were of LR grade and purchased from Loba Chemie Ltd., Mumbai 400 005, India. The microbial strains were obtained from the institute of microbial technology sector 39-A, Chandigarh, India. The melting point were determined in open capillary tubes and are uncorrected. The Purity of the compounds were checked on Silica gel-G coated plates were used for TLC, spots were visualized by exposure of iodine vapour in an iodine chamber. The structures of all the new synthesized compounds were confirmed by elemental analysis, IR and 1H NMR spectral data. IR spectra were recorded on a Shimadzu 8201 PC FTIR (umax in cm-1) using KBr discs and 1H NMR on a Bruker AV II in CDCl3 and DMSO-d6 at 400 MHz using TMS as an internal standard.

Synthesis of 1-Chloroacetyl-2-mercaptobenz-oxazole 2MB-1

An equimolar solution of 2-mercaptobenzoxazole 30g (0.2 mol) and chloroacetyl chloride 15.9 mL (0.2 mol) in chloroform (100 mL) in the presence of anhydrous potassium carbonate (2g) was refluxed on a water bath for about 5 hours. The solvent was removed under reduced pressure and the solid was purified by recrystallization from methanol. Yield 78.35%; mp 207-209 ^{0}C; IR (KBr): 3050, 1460, 880, 720 (indicated aromatic ring) and 2950, 2845 (CH2), 920 (C-O-C), 680 (C-S-C). 1H NMR (400 MHz): δ 7.17-7.67 (m, 4H, Ar-H) and 4.13 (s, 2H,-CH2).

Synthesis of 1-Hydrazino acetyl-2-mercaptobenzoxazole 2MB-2

A mixture of 1-chloroacetyl-2-mercaptobenzoxazole 22.7g (0.1mol) and hydrazine hydrate 4.9mL (0.1mol) in ethanol (50mL) was refluxed on a water bath for about 5 hours. After cooling the solvent was removed under reduced pressure and the residue was dried. The resulting solid was recrystallized from mixture of chloroform: methanol (1:2). Yield 67.77%; mp 230-231^{0}C; IR (KBr): 3320 (NHNH2) and 3400 (CH2NH). 1H NMR: δ 7.08-7.59 (m, 4H, Ar-H), 4.01 (s, 2H, -CH2), 5.54 (s, 1H, NH) and 4.79 (s, 1H, NH2).

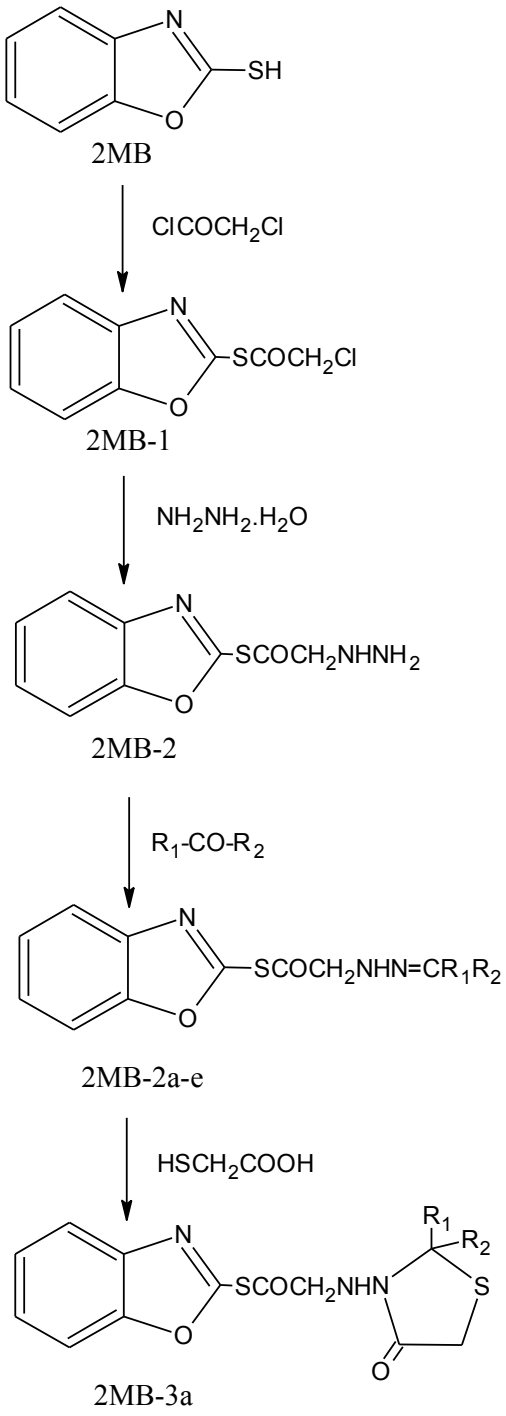
Synthesis of 1-[α-(Arylidine hydrazino) acytyl]-2-mercaptobenzoxazole 2MB-2a

A mixture of 1-hydrazino acetyl-2-mercaptobenzoxazole 2.23g (0.01mol) and 4-hydroxy benzaldehyde1.22g (0.01mol) and 2-3 drops of glacial acetic acid in methanol (30mL) was refluxed on a water bath for about 3 hours. After cooling the solvent was removed under reduced pressure and the residue was dried, the resulting solid was recrysatllized from mixture of chloroform: methanol (1:1).Yield 72.31%; mp: 240-241oC; IR (KBr): 1540 (N=C) and 3500 (OH). 1H NMR: δ 7.01-7.61 (m, 8H, Ar-H), 3.72 (s, 2H, -CH2), 6.17 (s, 1H, NH), 4.89 (s, 1H, N=CH). Other compounds 2-MB-2b-e were prepared in the similar way using compound 2MB-2 and various aromatic aldehydes. Physical and analytical data of compounds (2MB-2a-e) are given in table 1.

Synthesis of 2-[(4- Hydroxyphenyl) - 3 - (acetylamino)-1, 3- thiozolidine-4-one] - 2-mercaptobenzoxazole (2MB-3a)

A mixture of 1-[α-(4-Hydroxybenzylidine hydrazino) acetyl] -2-mercaptobenzoxazole 3.27g (0.01 mol) and thioglycolic acid 2.3 mL (0.01 mol) and in ethanol (25 mL) in presence of zinc chloride was refluxed on a water bath for 5 hours. After cooling the solvent was removed under reduced pressure and the residue was dried. The resulting solid was recrysatllized from mixture of chloroform: methanol (1:1). Yield 65.23%; mp: 268-270 ^{0}C; IR (KBr): 1715 (C=O cyclic), 3500 (Ar-OH). 1H NMR: δ 6.02-7.32 (m, 8H, Ar-H), 2.59 (s, 2H,-CH$_2$), 7.59 (s, 1H, NH), 3.59 (s, 1H, N-CH), 4.02 (s, 1H, OH) and 2.88 (s, 2H, -SCH$_2$).

Scheme for Synthesis



Antimicrobial Activity

All the newly synthesized compounds were screened for their antimicrobial activity against Gram-positive bacterium *Bacillus subtilis, Streptomyces griseus* and Gram-negative bacterium *Escherichia coli* using Rifampicin as a standard and for antifungal activity against *Ashbya gossypii* and *Aspergillus niger* using Fluconazole as a standard and using agar plate diffusion method[10]. DMF was run as control and the test was performed at 50 µg/mL, 100µg/mL and 500µg/mL concentration.

RESULTS AND DISCUSSION

All the newly synthesized compounds were screened for their antimicrobial activity against Gram-positive bacterium *Bacillus subtilis* (MTCC 441), *Streptomyces griseus* (MTCC 1540) and Gram-negative bacterium *Escherichia coli* (MTCC 443) using Rifampicin as a standard for antibacterial activity and for antifungal activity against *Ashbya gossypii* (MTCC 358) and *Aspergillus niger* (MTCC 282) using Fluconazole as a standard drug and using nutrient agar and Sabouraud's dextrose agar as a culture medium for antibacterial and antifungal activity respectively . DMF was run as control and the test was performed at 50µg/mL, 100µg/mL and 500µg/mL concentrations. The zones of inhibition were measured

in millimeters (<9 mm,9-11 mm,12-16 mm, 17-21 mm, 22-28 mm for inactive, very weak, weak, moderate and highly active zones respectively). Rifampicin exhibited a zone of inhibition of 25 mm for *E. coli*, 28 mm for *B. subtilis* and 27 mm for *S. griseus* at 500 ppm concentration. Fluconazole exhibited a zone of inhibition 28 mm for *Ashbya gossypii* and 26 mm for *Aspergillus niger* at 500 ppm concentration. The screening results revealed that the compounds 2MB-2d, 2MB-2e and 2MB-3a exhibited highest activity towards *E. coli* and *B. subtilis* while compounds 2MB-2a, 2MB-2e and 2MB-3a exhibited highest activity towards *Streptomyces griseus* while compounds 2MB-2b exhibited weak activity towards *E. coli*,

Streptomyces griseus and *B. subtilis.* The compound 2MB-2c shown weak activity towards *E .coli* and rest of compounds moderate active towards used bacteria. The results of antifungal activity of the test compounds were found to be somewhat different from their antibacterial activity. The compounds 2MB-2a, 2MB-2d, 2MB-2e and 2MB-3a exhibited highest activity towards *A. niger* and *A. gossypii* while compound 2MB-2b showed weak activity towards *A. niger* and *A. gossypii* and compound 2MB-2c displayed weak activity towards *A. gossypii* at 500 ppm concentration and rest of compounds displayed moderate activity towards both fungi.

Introduction of thiazolidine ring in above compounds enhanced the activity. Thus it was concluded that for all Schiff bases of benzoxazole derivatives, antibacterial and antifungal activity decreases when there is no substitution and o-substitution in benzylideneamino group and it increases with p-substitution showing maximum activity by hydroxy group and dimethylamino group attached to para position of benzylideneamino group.

Table 1: Physical properties of compounds

S. No.	Compounds	R_1	R_2	Mol. Formula	Mol. Wt.	Yield (%)	m.p.(°C)
1	2MB-2a	H	4-OHC_6H_4	$C_{16}H_{13}N_3O_3S$	327.48	72.31	240-241
2	2MB-2b	H	C_6H_5	$C_{16}H_{13}N_3O_2S$	311.25	67.23	217-218
3	2MB-2c	H	2-$NO_2C_6H_4$	$C_{16}H_{12}N_4O_4S$	356.22	62.44	261-263
4	2MB-2d	H	3-$NO_2C_6H_4$	$C_{16}H_{12}N_4O_4S$	356.22	58.69	249-250
5	2MB-2e	H	4-$N(CH_3)_2C_6H_5$	$C_{18}H_{18}N_4O_2S$	354.44	69.55	233-234
6	2MB-3a	H	4-OHC_6H_4	$C_{18}H_{15}N_3O_4S_2$	401.18	65.23	268-270

Table 2: Antibacterial activity of compounds (2MB-2a-e) and (2-MB-3a)

Bacterial strains	***E .coli***			***B.Subtilis***			***S. griseus***		
Conc. (In ppm)	**50**	**100**	**500**	**50**	**100**	**500**	**50**	**100**	**500**
Compd.									
2MB-2a	+	++	+++	+++	+++	++++	++	++	++
2MB-2b	-	++	+++	+	+++	+++	++	+++	+++
2MB-2c	++	+++	+++	-	++	++++	++	+++	+++
2MB-2d	+	++	+++	+++	+++	+++	++	++	+++
2MB-2e	++	++	++++	++	+++	++++	+++	+++	+++
2MB-3a	+++	+++	++++	+++	++++	+++	+++	+++	++++
RC	+++	++++	++++	+++	++++	++++	+++	++++	++++

RC = Rifampicin; Zone of inhibition (diameter) in mm (-) < 9, (+) 9-11, (++) 12-16, (+++) 17-21 and (++++) 22-28.

Table 3: Antifungal activity of compounds (2MB-2a-e) and (2-MB-3a)

Fungal strains	***A.niger***			***A. gossypii***		
Conc.	50 ppm	100 ppm	500 ppm	50 ppm	100 ppm	500 ppm
Compd.						
2MB-2a	++	+++	++++	++	++	+++
2MB-2b	+	++	++	-	+	++
2MB-2c	++	+++	+++	++	+++	+++
2MB-2d	+	+++	+++	++	++	+++
2MB-2e	++	+++	++++	+++	+++	++++
2MB-3a	+++	+++	++++	++	+++	++++
FA	+++	++++	++++	+++	++++	++++

FA = Fluconazole; Zone of inhibition (diameter) in mm (-) < 9, (+) 9-11, (++) 12-16, (+++) 17-21 and (++++) 22-28.

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