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Research Article

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF N-SUBSTITUTED-ARYL/ALKYLIDENE HYDRAZINO CARBONYL METHYL DERIVATIVE OF 2, 3-DIHYDRO-3-OXO-1, 4-BENZOTHIAZINE

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ABSTRACT

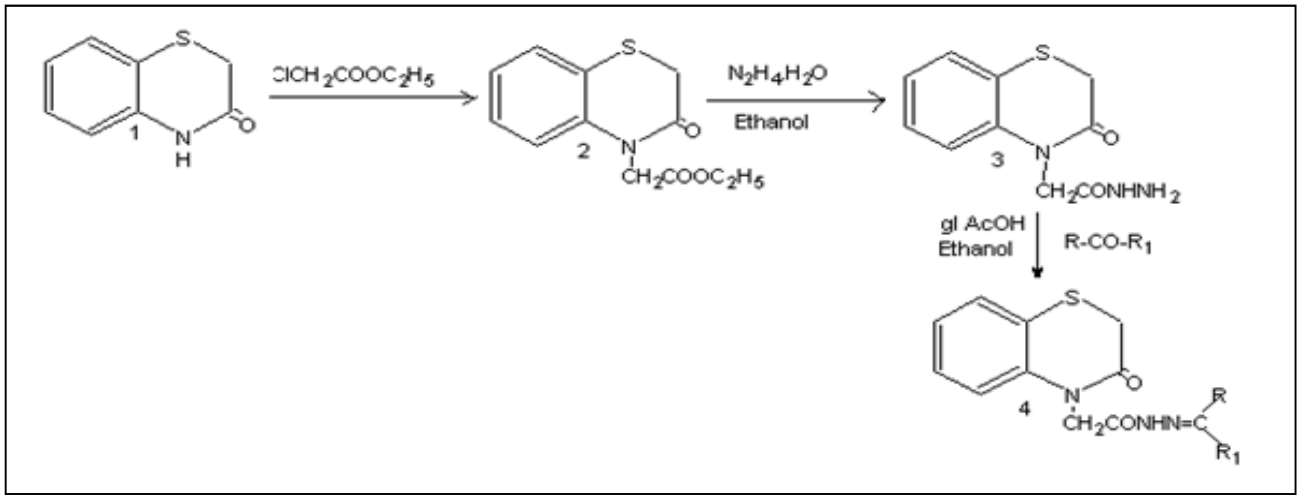
A series of N-substituted Aryl/Alkyllidine hydrazino carbonyl methyl derivative of 2,3-dihydro-3oxo-1, 4-benzothiazine has been synthesized by appropriate method. All the compounds have been screened for their antifungal activity against Candida albicans,Penicillium and Aspergillus niger, antibacterial activity against Bacillus subtillis, Streptococcus venezuela, S.gresious and Escherichia coli. In the primary screening some of the compounds exhibited appreciable activity. The structure of the synthesized compound 4 a-m has been established on the basis of elemental analysis and spectral data.

KEY WORDS: Benzothiazine, antifungal, antibacterial activity.

INTRODUCTION

2, 3-dihydro-3-oxo-1, 4-benzothiazine derivatives are known to possess varius biological activities such as anti-inflammatory[1-9], anthelmintic, antifungal and CNS depressants[11-15]. Encouraged by these reports and also in continuation of our interest in the 2, 3-dihydro-3-oxo-1, 4-benzothiazinederivatives. Chemo selectivity of 2, 3-dihydro-3-oxo-1, 4-benzothiazine carboxylates towards hydrazine hydrate, it was planned to enhance the activity. Hence in present study the 4th position of 1, 4-benzothiazine moiety having –NH group was used as the target for chemical change (**Scheme I**). These observations promoted us to **(1-4)** as per **Scheme I** with a view to evaluate their antibacterial and antifungal activity.

Scheme-1: scheme showing the synthesis of N-substituted-Aryl/Alkylidene hydrazino carbonyl methyl derivative of 2, 3-dihydro-3-oxo-1, 4-benzothiazine



MATERIALS AND METHODS

All the chemicals used were obtained from S.D. Fine Chem. Ltd., Mumbai and E-Merck Ltd., Mumbai while the reagents and solvents were of analytical grade. The melting points were carried out in open capillary tube and were uncorrected. Thin layer chromatography was performed using silica gel coated on a glass plate. IR spectra in KBr disc and the absorption bands are expressed in cm-1 were recorded on a Shimadzu 8201 PC FTIR spectrophotometer. 1H NMR spectra were recorded in CDCl3+acetone-d6 on a FX 90Q FTNMR spectrometer using TMS as an internal standard (chemical shifts in δ, ppm). The reactions were monitored by thin layer chromatography on silica gel G coated glass plates using benzene: ethyl acetate (7:3) solvent system. The purity of synthesized compounds was ascertained by TLC using iodine vapours as detecting agents

The starting 2, 3-dihydro-3-oxo-1, 4-benzothiazine 1 was prepared by literature method.1-ethoxy carbonyl methyl-2, 3-dihydro-1,4-benzothiazine 2 prepared from condensation of compound 1 with ethylchloroactate in dry acetone. The compound 2 on ammonolysis with hydrazine hydrate in ethanol yielded 1-hydrazino carbonyl methyl-2, 3-dihydro-3-oxo-1, 4-benzothiazine 3.

Compound 3 underwent condensation with different carbonyls to afford the aryl/alkylidene hydrazino carbonyl methyl 2,3-dihydro-1, 4-benzothiazine (scheme I Table I). All the compounds Synthesized were adequately characterized by their elemental analysis and spectral IR and NMR data.

4[1-Ethoxy carbonyl methyl] 2,3-dihydro-3-oxo-1, 4-benzothiazine 2:

equimolar solution of 2,3-dihydro-3-oxo-1,4-benzothiazine (0.01 mole) and ethyl chloroacetate (0.01 mole) in dry acetone (40 ml) in the presence of anhydrous K2CO3 (5 g) was refluxed on a water-bath for about 16 hr. the solvent was removed in vacou and the residue was recrystalised from chloroform to furnish compound 2, yied 86%,mp 217-2190C. Anal. Calcd for C12H13O3NS: C, 60.74; H, 5.52; N, 10.60 Found: C, 60.72; H, 5.49 N, 10.64% IR: cm-1, 3023, 1510, 1105, 1070, 1033, 638 (aromatic ring), 172 (>C=O of ester), 1675 (C-N), 1225 and 1044 (C-O-C), 720 (C-S-C) and 2910, 2870, 1425 and 715 (CH2); 1HNMR: δ, 1.25 (t, 3H, J=7Hz. –COOCH2CH3), 4.10 (q, 2H,

J=7Hz –COOC2H5), 4.48 (s, 2H, S-CH2) and 6.70-7.90 (m, 4H, Ar-H)

4[Hydrazino carbonyl methyl] 2,3-dihydro-3-oxo-1, 4-benzothiazine 3:
4[1-Ethoxy carbonyl methyl] 2,3-dihydro-3oxo-1, 4-benzothiazine (0.1 mole) and hydrazine hydrate (0.1 mole) in methanol (30 ml) was refluxed for about 5 hr on a steam bath. After cooling the resulting solid was filtered, dried and recrystalised from ethanol to get compound 3, yield 87%, mp 211-2130C. Anal. Calcd for C10H11N3O2S: C, 50.62; H, 4.67 N, 17.71; Found: C, 50.64; H, 4.54 N, 17.61%; IR: cm-1 3355, 3382 (-NHNH2) and 1661 (C=O of amide); 1HNMR: δ, 6.85-7.96 (m, 4H, aromatic ring), 4.41 (s, 2H, NH2), 4.85 (s,2H,S-CH2) and 7.85 (s,1H,-CONH).

4[Aryl/alkylidene- hydrazino carbonyl methyl] 2,3-dihydro-3oxo-1, 4-benzothiazine 4:
a mixture of compound 3 (0.003 mole) and 3-benzaldehyde (0.003 mole) and 2-3 drops of gl. acetic acid in ethanol (25 was ml) was refluxed on a water bath for about 6 hr. The solvent was removed and residue was recrystalised from chloroform methanol mixture to get compound 3, yield 85%, mp 148-1500C. Anal. Calcd for C17H15N3O2S. C, 62.75; H, 4.65; N, 12.91; Found C, 62.57; H, 3.97; N, 12.50%; IR: cm-1, 3342 and 1335 (-NH-), 1665(>C=O), 1625 (-N=CH-); 1HNMR: δ, 4.45 (1H, s, N=CH), 8.15 (1H,s, CONH), 6.90,7.70 (m, 4H, aromatic ring).

Other compounds 4b-m were synthesized similarly. Characterization data are presented in Table I

Compd	R	R_1	m.p. ^{0}C	Yield	Mol. formula	found (%) (Calcd) C H N
4a	C_6H_5	H	201-203	79	$C_{17}H_{15}N_3O_2S$	62.75 4.65 12.91
4b	4-OH-C_6H_4	H	197-199	72	$C_{17}H_{16}N_3O_3S$	58.82 3.68 8.53
4c	4-CH_3-C_6H_4	H	206-208	68	$C_{18}H_{18}N_3O_3S$	58.52 3.68 8.53
4d	4-Cl-C_6H_4	H	168-170	70	$C_{17}H_{15}Cl_3O_2S$	66.15 5.18 5.14
4e	$(CH_3)_2$-N-C_6H_4	H	294-296	79	$C_{19}H_{22}N_4O_2S$	67.34 6.00 9.82
4f	-CH=CH-C_6H_4	H	184-186	69	$C_{19}H_{17}N_3O_2S$	69.39 4.99 5.78
4g	4-NH_2-C_6H_4	CH_3	210-212	68	$C_{18}H_{17}N_3O_2S$	69.39 4.99 5.78
4h	C_2H_5	CH_3	220-222	74	$C_{14}H_{17}N_3O_2S$	58.52 3.68 8.53
4i	-CH=CH-CH_3	H	232-234	63	$C_{14}H_{18}N_3O_2S$	58.32 4.89 14.57
4j	CH_3	C_5H_4N	254-256	62	$C_{17}H_{16}N_4O_2S$	64.17 4.56 11.57
4k	-CH_2-CH(CH3)$_2$	CH_3	194-196	78	$C_{16}H_{21}N_3O_2S$	58.52 3.68 8.53
4l	C_5H_4N	H	165-167	69	$C_{16}H_{14}N_4O_2S$	64.17 4.56 11.51
4m	4-NO_2-C_6H_4	H	148-150	85	$C_{17}H_{14}N_4O_4S$	58.52 3.86 9.56

Table I-Characterization data of compound 4 a-m

ANTIMICROBIAL ACTIVITY:
All the newly synthesized compounds were screened for their antimicrobial activity against gram-positive bacterium streptococcus and gram-negative bacterium Escherichia coli using Norfolxacin as a standard and for the antifungal against Pencillium and Aspergillus niger using nutrient agar as culture medium.
The zone of inhibition were measured in mm (10-14 mm, 14-18 mm, 18-22mm for weak, moderate and highly active zones respectively) Norfloxacine showed a zone of inhibition of 20 mm for S.venezuala and 18 mm for S.gresious Ketakonazole exhibited a zone of inhibition 18 mm for Penicillium and 19 mm for Aspergillus niger. The screened activity revealed that the compounds 4g, 4k and 4i exhibited highly activity towards B. subtilis, S.venezuala and S.gresious while the compounds 4f, 4h was

inactive towards S.gresious,while compounds 4d,4k, 4l, 4m displayed moderate activity towards B. subtilis, S.venezuala, rest of the compounds were weakly active towards S.venezuala and S.gresious. (Table II) Compounds 4a, 4k and 4m displayed highly activity towards Penicillium and A.niger. While the compound 4j displayed moderate activity towards C.albicans and weak activity towards Penicillium compound4h exhibited moderate activity towards C.albicans and weak activity towards Penicillium and rest of the compounds displayed weak or moderate activity towards C.albicans and Penicillium. (Table III)

	Zone of inhibition (mm)							
Compounds Code	***E.coli*** 50 ppm 100ppm		***B. subtilis*** 50 ppm 100ppm		***S.venezuala*** 50 ppm 100ppm		***S.gresious*** 50 ppm 100ppm	
4a	12	10	14	11	13	14	16	13
4b	12	14	11	13	10	14	12	11
4c	10	14	11	14	11	15	11	12
4d	13	12	10	11	12	11	14	12
4e	11	14	13	11	14	11	13	16
4f	10	14	13	11	12	10	9	13
4g	11	13	14	15	12	10	11	14
4h	12	14	11	10	11	12	9	13
4i	12	11	13	14	12	12	14	13
4j	10	11	14	15	11	13	10	11
4k	12	13	11	13	14	15	16	16
4l	12	11	10	14	16	14	11	13
4m	13	14	11	12	10	14	11	13
Norfloxacine	16	18	17	20	18	20	22	18

Table II: Antimicrobial activity of synthesized compounds:

	Zone of inhibition (mm)					
Compounds Code	***C.albicans*** 50 ppm 100ppm		***Penicillium*** 50 ppm 100ppm		***A.niger*** 50 ppm 100ppm	
4a	11	12	15	13	11	17
4b	10	11	13	14	10	14
4c	10	15	11	14	11	15
4d	11	13	10	12	11	14
4e	13	15	11	10	11	14
4f	12	14	10	14	12	13
4g	10	11	14	15	14	16
4h	12	16	11	10	11	12
4i	13	14	11	14	11	13
4j	11	16	10	13	13	15
4k	11	13	14	13	10	17
4l	13	14	10	14	11	14
4m	13	14	11	12	10	16
Ketakonazole	16	18	17	18	15	19

Table III: Antifungal activity of synthesized compounds:

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