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Research Article

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Novel synthesis and antimicrobial activity of bis-oxazine derivatives

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ABSTRACT

*A series of novel 2-[2-Amino-4(4-bromophenyl)-6H-1,3-oxazine-6-yl]-4-{3-[2-amino-4(4-bromophenyl)-6H-1,3-oxazine-6-yl]-4-hydroxybenzyl}phenol derivatives **[3a-3i]** were prepared from Bis[3-[(E)-3(4-bromophenyl)-3-oxo-1-propenyl]-4-hydroxyphenyl]methane **[2a-2i]** with urea and potassium hydroxide in ethanol. All synthesized compounds were characterized on the basis of IR,NMR spectroscopic data and Elemental Analysis. Antimicrobial activity were evaluated and compared with the standard drugs, some compounds of the series exhibited promising anti- bacterial and anti- fungal activity compared to standard drugs.*

Keywords: Synthesis, Bis-chalcone, Bis-oxazine, urea, antimicrobial activity

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INTRODUCTION

Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics [1]. Hence they have attracted considerable attention in the design of biological active molecules [2].A practical method for the synthesis of such compounds is of great interest in synthetic organic chemistry. Oxazine derivatives are an important class of heterocyclic compounds and they have reported claiming diversified biological activities, such as antimicrobial [3-8] and anticoagulant activities [9-10],anticancer[11,12], fungicidal [13] and anti-tubercular [14-18], ant malarial [19], analgesic, anti-inflammatory [20], antibacterial [21], antidiabetic and hypolipidaemic [22], antiproliferative [23] activities. Owing to the biological significance of oxazine compounds and continuation of our ongoing study on antimicrobial agent ,we planned to synthesize a combined molecular framework that involves these two same active pharmacophores and their increasing importance in pharmaceutical and biological field. Therefore a series of novel 2-[2-Amino-4(4-bromo phenyl)-6H-1,3-oxazine-6-yl]-4-{3-[2-amino-4(4-bromo phenyl)-6H-1,3-oxazine-6-yl]-4-hydroxy benzyl} phenol derivatives **[3a-3i]**has been synthesized and screened their antimicrobial activities.

EXPERIMENTAL SECTION

The melting points were recorded on electro-thermal apparatus and are uncorrected. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF254, 200 mesh) aluminium plates (E Merk) using hexane and ethyl acatate visualized in iodine chamber. IR spectra were recorded in KBr on a perkin-Elmer model-983. 1HNMR spectrum recorded on Varian Mercury 300MHz instrument using $CDCl_3$, DMSO-d_6 as solvent (chemical shift in δ ppm), using TMS as internal standard. Elemental analysis was performed on a Heracus CHN analyzer and was within the ±0.5% of the theoretical values.

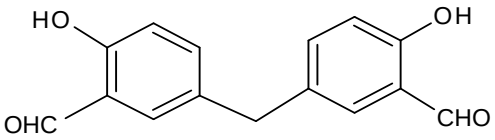
General Procedure for preparation of Bis[3-[(E)-3(4-bromophenyl)-3-oxo-1-propenyl]-4-hydroxyphenyl] methane derivatives [2a-2i]

A Solution of 5,5'-methylene-bis-salicylaldehyde **[1]** (0.01mol) and various substituted acetophenone (0.02mol) in 20 ml of ethanol was treated with 20 ml of 60% KOH solution at 5-10 ^{0}C. The reaction mixture was stirred at room temperature 3-4 h. It was then diluted with (50 ml) water and extracted with diethyl ether. The aqueous solution

was acidified with dilute HCl. The solid obtained was filtered washed thoroughly with water and dried. The crude product was recrystallized from benzene : methanol (3:2) to give compounds **2a-2i**.

General Procedure for preparation of 2-[2-Amino-4-(4-bromophenyl)-6H-1,3-oxazine-6-yl]-4-{3-[2-amino-4(4-bromophenyl)-6H-1,3-oxazine-6-yl]-4-hydroxybenzyl}phenol derivatives [3a-3i]

A solution of (0.01) Bis[3-[(E)-3(4-bromophenyl)-3-oxo-1-propenyl]-4-hydroxyphenyl]methane **[2a-2i]** and urea (0.03 mol) in 20ml ethanol was added 5 ml alcoholic KOH (0.02 mol). The reaction mixtutre was refluxed. TLC (ethyl acetate: hexane, 2:1) showed that the reaction was completed in 5 h. The reaction mixture was poured in 50 ml of 10% HCl solution (cold) and the precipitate was filtered, washed with water until free from acid and recrystallized from benzene – ethanol.



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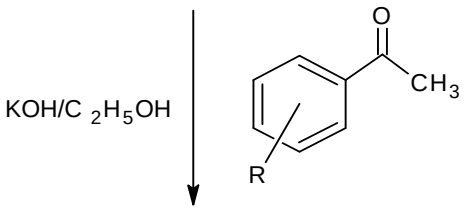
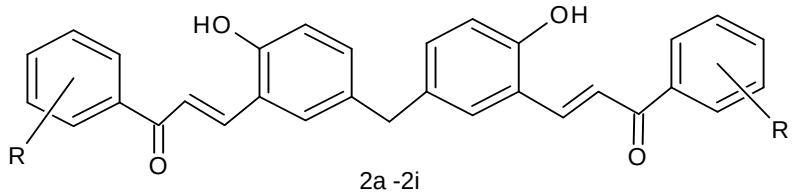
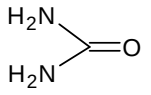
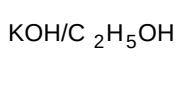
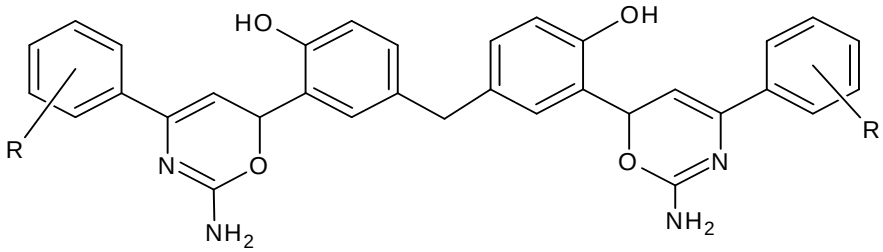




2a -2i







3a -3i

Table 1: Physical and Elemental analysis of Synthesized compounds(3a-3i):

Comp No	M.F	R	M.P ^{0}C	Yield %	Elemental analysis					
					%C	%H	%N	%O	%Br	%Cl
3a	$C_{33}H_{26}Br_2N_4O_4$	4-Br-	135	77	55.2	3.41	6.94	8.97	22.1	-
3b	$C_{35}H_{32}N_4O_6$	4-OCH_3	107	72	69.1	4.97	8.76	15.3	-	-
3c	$C_{33}H_{26}Cl_2N_2O_4$	4- Cl	120	80	64.3	3.99	8.97	10.2	-	11.1
3d	$C_{33}H_{26}Cl_2N_2O_4$	2-Cl	157	71	64.1	4.10	8,90	10.1	-	11.3
3e	$C_{33}H_{28}N_4O_6$	4- OH	129	75	68.3	4.39	9.39	15.4	-	-
3f	$C_{33}H_{28}N_4O_6$	2-OH	145	77	68.2	4.46	9.35	15.9	-	-
3g	$C_{33}H_{26}N_6O_8$	4- NO_2	103	73	61.9	3.77	12.9	19.7	-	-
3h	$C_{33}H_{26}N_6O_8$	2-NO_2	138	79	61.9	3.34	12.6	19.8	-	-
3i	$C_{33}H_{30}N_6O_4$	4-NH_2	141	77	67.7	4.21	14.1	10.5		

Table 2: Spectral Data of Synthesized Compounds (3a-3g)

Comp. No.	IR(KBr) V(cm^{-1})	1H NMR ($CDCl_3$) δ in ppm
3a	3261(NH), 3326(OH), 3035(CH), 1623(C=N), 1593, 1473(ArC=C)	3.85(s,NH_2),3.32(s,OH),4.75(d,CH),6.83(d,CH),7.29-8.03 (m, ArH).
3b	3267(NH), 3326(OH), 3039(CH), 1623(C=N), 1597, 1471(ArC=C)	3.87(s,NH_2),3.32(s,OH),4.71(d,CH),6.74(d,CH),7.26-8.07 (m, ArH).
3c	3260(NH), 3321(OH), 3040(CH), 1626(C=N), 1595, 1475(ArC=C).	3.81(s,NH_2),3.32(s,OH),4.69(d,CH),6.64 (d,CH),7.26-8.02 (m, ArH).
3d	3266(NH), 3329(OH), 3040(CH), 1623(C=N), 1597, 1481(ArC=C).	3.82(s,NH_2),3.32(s,OH),4.73(d,CH),6.69(d,CH),7.26-8.09 (m, ArH).
3e	3263(NH), 3326(OH), 3037(CH), 1623(C=N), 1591, 1476(ArC=C).	3.86(s,NH_2),3.34(s,OH),4.71(d,CH),6.9(d,CH),7.29-8.07 (m, ArH).
3f	3264(NH), 3329(OH), 3042(CH), 1620(C=N), 1595, 1473(ArC=C).	3.85(s,NH_2),3.32(s,OH),4.73(d,CH),6.93(d,CH),7.26-8.07 (m, ArH).
3g	3249(NH), 3325(OH), 3041(CH), 1627(C=N), 1593, 1479(ArC=C).	3.77(s,NH_2),3.32(s,OH),4.77(d,CH),6.95(d,CH),7.26-8.04 (m, ArH).
3h	3257(NH), 3326(OH), 3039(CH), 1626(C=N), 1595, 1477(ArC=C).	3.79(s,NH_2),3.32(s,OH),4.75(d,CH),6.90(d,CH),7.26-8.02 (m, ArH).
3i	3262(NH), 3329(OH), 3040(CH), 1623(C=N), 1597, 1475(ArC=C).	3.83(s,NH_2),3.32(s,OH),4.76(d,CH),6.85(d,CH),7.26-8.04 (m, ArH).

Antimicrobial activity:

The synthesized compounds (3a-3i) were screened for their in vitro antimicrobial activity by using cup plate method[24]. Antibacterial activity was screened against two gram positive bacteria *Staphylococcus aureus, Bacillus subtilis* and two gram negative bacteria *Escherichia coli, Pseudomonas aeruginosa* by measuring the zone of inhibition on agar plates at concentrations 100 µg/mL. Antifungal activity was screened against *Candida albicans, Aspergillus niger* by measuring the zone of inhibition on agar plates at concentrations 100 µg/mL and reported in Table-3. Nutrient agar was employed as culture medium and DMSO was used as solvent control for antimicrobial activity. Streptomycin and griseofulvin were used as standard for antibacterial and antifungal activities respectively.

Table 3: Antimicrobial activity of Synthesized Compounds

Comp. (100µg/ml)	Antibacterial				Antifungal	
	S. Aureus	*B. Subtilis*	*E. Coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
3a	15	19	20	14	12	15
3b	13	17	21	17	11	17
3c	04	09	13	05	11	13
3d	14	18	17	13	20	17
3e	13	15	19	17	10	12
3f	05	07	03	05	05	07
3g	06	04	05	09	10	15
3h	10	15	17	13	03	05
3i	10	07	04	06	09	03
Streptomycin	17	20	22	19	-	-
Griesofulvin	-	-	-	-	21	17

RESULTS AND DISSCUSSION

All the synthesized compounds were characterized by IR and ^{1}HNMR spectroscopy. Spectral data are shown in table 2. Further screened for their antibacterial and antifungal activity by using cup-plate method. The antibacterial and antifungal activity of each compound was compared with standard drug Streptomycin and griseofulvin.

Antibacterial Activity

The antibacterial activity are shown in Table 3. The Compounds **3a, 3b, 3d, 3e, 3h** exhibited good activity against gram-positive bacteria *S. aureus, B. subtilis* and gram-negative bacteria *E. coli, P. aeruginosa*. While other compounds **3c, 3f, 3g, 3i,** exhibited moderate to poor activity against the tested microorganisms, compared to standard drug.

Antifungal Activity

The antifungal activity are shown in Table 3. The Compounds **3a, 3b, 3c, 3d, 3e, 3g,** showed good activity against *C. albican , A. niger.* while the remaining compounds **3f, 3h, 3i** exhibited moderate to poor activity as compared to standard drug Streptomycin and griseofulvin. As we consider all results obtained from antibacterial and antifungal tests together we can say that entire compounds tested are active towards bacteria and fungi.

CONCLUSION

In conclusion, we have synthesized novel 2-[2-Amino-4(4-bromophenyl)-6H-1,3-oxazine-6-yl]-4-{3-[2-amino-4(4-bromophenyl)-6H-1,3-oxazine-6-yl]-4-hydroxybenzyl}phenol derivatives **[3a-3i]**. then characterization and tested for their antimicrobial activities against various types of bacteria and fungi. The results reveal that some of the compounds of the series exhibited promising antibacterial and antifungal activity compared to standard drugs.

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