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Research Article

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Synthesis and antimicrobial activity of thiazine derivatives

Sayaji S. Didwagh and Pravina B. Piste*

P. G. Department of Chemistry, Yashavantrao Chavan Institute of Science, Satara, Maharastra, India

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ABSTRACT

*A series 2-[4-(2-amino-6-phenyl-6H-1,3-thiazin-4-yl)phenoxy]ethanol derivative **(4a-4g)** were synthesized from 1-[4-(2-hydroxyethoxy)phenyl]-3-phenylprop-2-en-1-one **(3a-3g)** with thiourea And sodium hydroxide in ethanol. All the synthesized compounds characterized on the basis of their IR, 1H NMR spectroscopic data and elemental analysis. All the compounds have been screened for antimicrobial activity by the cup-plate method.*

Keywords: Synthesis, Chalcones, aldehyde, thiazines, Antimicrobial activity.

INTRODUCTION

Hetrocycles are abundant in nature and involved synthesis of pharamaceuatical and biological important molecules. Thiazines and their derivatives are played important role in hetrocyclic chemistry. A large number thiazine derivatives also exhibited various biological activities such as antimicrobial [1], anti-inflammatory [2],antioxidant [3],antipyretic[4] ,antitumor [5], calcium channel modulators [6]. The Chalcones have been used as intermediates for synthesis of various heterocyclic compounds.Literature review reveals that chalcones exhibited various biological and pharamacological activities such as antimicrobial [7],antifungal [8] , analgesic [9], anti-platelet [10],insecticidal [11], anti-malarial[12], antiviral[13] activities. In view of these observations and in continuation of our work on biologically active hetrocycles and their increasing importance in pharamaceuatical and biological field[14]. The synthesis of the new antibacterial,antifungal agents to help in the battle against pathogenic microorganisms. Therefore ,we synthesized new 2-[4-(2-amino-6-phenyl-6*H*-1,3-thiazin-4-yl)phenoxy]ethanol derivatives and evaluated their biological 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.

Procedure for preparation of potassium salt of p-hydroxy acetophenone (1)
To an ethanolic solution of KOH (5.4 g in 72ml) ,p-hydroxy acetophenone (10 g) was added with stirring. The solution was stirred at room temperature for 1-2 hr and concentrated under reduced pressure. Diethyl ether (40 ml) was added to it. Solid of potassium salt of p-hydroxy acetophenone was separated out. It was washed with diethyl ether and kept for drying in a desiccator under vacuum.

Preparation of 1[4-(2-hydroxy- ethoxy) phenyl] ethanone (2)
2-Chloroethanol (5.52 ml) was added in potassium salt of p - hydroxy acetophenone (10 g) suspended in dry DMF (20 ml).The mixture of flaske were refluxed in the oil bath at 80 -90 ^{0}C for 18 hr under anhydrous conditions. The

reaction was monitored by thin layer chromatography. After the removal of DMF under vacuum.The resulting product was purified by passing it through a chromatographic column pacted with silica gel using hexane : ethyl acetate (4;3) as eluant.Resulting purified product was recrystallized by ethanol to give compound **2**.

Preparation of (2E)- 1-[4-(2-hydroxyethoxy)phenyl]-3-phenylprop-2-en-1-one (3a-3g)

A mixture of 1[4-(2-hydroxy- ethoxy) phenyl] ethanone (0.01 mol) and various aromatic aldehyde (0.01mol) were dissolved in ethanol (25 ml), under stirring aq.NaOH (50%, 12 ml) was added drop wise. The reaction mixture was stirred at room temperature and kept overnight in a bulb oven at 55-60 ^{0}C. Then the reaction mixture was poured into ice water and then acidified the product with 10%HCl solution in cold condition. The chalcone derivative precipitates out as solid. Then it was filtered,washed with cold water and recrystallized from ethanol to give compounds **3a-3f**.

Preparation of 2-[4-(2-amino-6-phenyl-6*H*-1,3-thiazin-4-yl)phenoxy]ethanol derivatives (4a-4g):

A mixture of chalcone(0.02mol), thiourea(0.02mol) were dissolved in ethanolic NaOH (25ml) was stirred about 2-3 hours with a magnetic stirrer. This was then poured into 400ml of cold water with continuous stirring for an hour & then kept in refrigerator for 24 hours. The separated solid was filtered,washed and recrystallized from ethanol. The completion of the reaction was monitored by TLC.

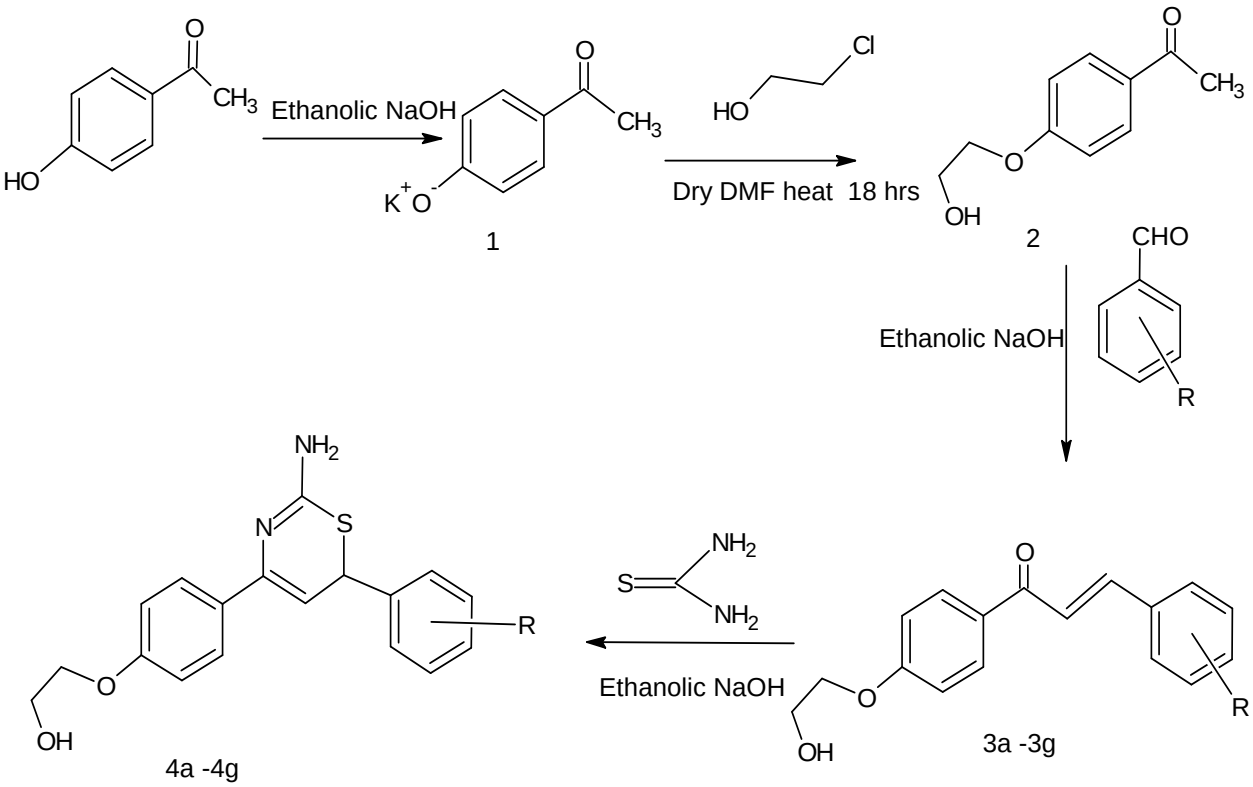

Table 1: Physical and Elemental analysis of Synthesized compounds(4a-4g):

Comp. No.	M.F	R	M. P. ^{0}C	Yield %	Elemental analysis					
					%C	%H	%N	%O	%S	%Cl
4a	$C_{18}H_{18}N_2O_2S$	C_6H_5	117	53	66.1	5.30	8.56	9.60	9.80	-
4b	$C_{19}H_{20}N_2O_3S$	4-$OCH_3C_6H_4$	109	69	64.0	5.60	7.76	13.4	8.96	-
4c	$C_{18}H_{17}ClN_2O_2S$	4- Cl C_6H_4	89	74	59.4	4.35	7.70	8.21	8.48	9.3
4d	$C_{18}H_{17}ClN_2O_2S$	2-Cl C_6H_4	137	49	59.8	4.61	7.40	8.80	8.61	9.1
4e	$C_{18}H_{18}N_2O_3S$	4- OH C_6H_4	96	57	62.2	4.90	7.82	13.9	8.97	-
4f	$C_{20}H_{23}N_3O_2S$	4.N$(CH_3)_2C_6H_4$	75	71	64.6	6.12	11.0	8.21	8.68	-
4g	$C_{18}H_{17}N_3O_4S$	4- NO_2 C_6H_4	113	66	57.8	4.10	10.2	17.0	8.15	-

Table 2: Spectral Data of Synthesized Compounds (4a-4g):

Comp. No.	IR(KBr) V(cm^{-1})	1H NMR ($CDCl_3$) δ in ppm
4a	3340.3(OH), 3033(CH), 1621(1^0NH_2, 1253 (C-S-C), 1471(Ar, C=C), 1020.0 (C-O).	2.32(s, OH), 4.17 (dd, CH_2), 2.41(s, Ar-NH_2), 5.74 (d, CH), 6.93(d, CH).
4b	3361.3(OH), 3075(CH), 1634(1^0NH_2, 1257 (C-S-C), 1479(Ar, C=C), 1043.0 (C-O).	2.35(s, OH), 4.15 (dd, CH_2), 2.57(s, Ar-NH_2), 5.79 (d, CH), 6.91(d, CH).
4c	3369.3(OH), 3010(CH), 1618(1^0NH_2, 1253 (C-S-C), 1484(Ar, C=C), 1047.0 (C-O).	2.83(s, OH), 4.21 (dd, CH_2), 2.34(s, Ar-NH_2), 5.64 (d, CH), 6.89(d, CH).
4d	3362.3(OH), 3025(CH), 1611(1^0NH_2, 1251 (C-S-C), 1489(Ar, C=C), 1055.0 (C-O).	2.65(s, OH), 4.19 (dd, CH_2), 2.62(s, Ar-NH_2), 5.71 (d, CH), 6.93(d, CH).
4e	3383.3(OH), 3044(CH), 1626(1^0NH_2, 1237 (C-S-C), 1509(Ar, C=C), 1035.0 (C-O).	2.91(s, OH), 4.37 (dd, CH_2), 2.89(s, Ar-NH_2), 5.67 (d, CH), 6.90(d, CH).
4f	3329.3(OH), 3053(CH), 1613(1^0NH_2, 1265 (C-S-C), 1497(Ar, C=C), 1026.0 (C-O).	2.69(s, OH), 4.16 (dd, CH_2), 2.55(s, Ar-NH_2), 5.77 (d, CH), 6.93(d, CH).
4g	3394.3(OH), 3067(CH), 1619(1^0NH_2, 1246 (C-S-C), 1516(Ar, C=C), 1031.0 (C-O).	2.74(s, OH), 4.23 (dd, CH_2), 2.91(s, Ar-NH_2), 5.73 (d, CH), 6.89(d, CH).

Antimicrobial activity

The synthesised compounds (4a-4f) were screened for their in vitro antimicrobial activity by using cup plate method[15]. 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*
4a	14	10	06	07	10	08
4b	08	05	11	09	21	13
4c	16	09	21	11	07	09
4d	15	11	20	04	11	04
4e	05	07	10	09	18	16
4f	07	20	09	19	17	15
4g	09	19	12	18	20	17
Streptomycin	17	20	22	19	-	-
Griesofulvin	-	-	-	-	21	17

RESULTS AND DISCUSSION

The structure of all synthesized compounds are confirmed by IR, 1H NMR spectroscopy. Spectral data are shown in table 2 .The compounds were evaluated for their antimicrobial activity. Most of the compounds exhibited good to moderate antitbacterial and antifungal activity against the tested microorganisms. The antibacterial activity are shown in Table 3. The Compound **4a** (R =H) displayed good activity against *S. aureus* and compounds **4c** (4 -Cl) , **4d** (2-Cl) showed good activity against *S. aureus* and *E. coli* while compound **4f** (R = 4-$N(CH_3)_2$,**4g (** 4- NO_2) possessed good activity against *B. subtilis* and *P. aeruginosa* as compared to standard drug Streptomycin and griseofulvin. The remaining compounds **4b** (R = 4-OCH_3),**4e** (4- OH) exhibited moderate activities as compared to standard drugs. The antifungal activity are shown in Table 3. The Compounds **4b**(R =OCH_3) **4e** (4 –OH) , **4f** (4-$N(CH_3)$, **4g** (4-NO_2) showed good activity against *Candida albican , Aspergillus niger.* while The remaining compounds exhibited moderate activities as compared to standard drugs. 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

The present work involved the synthesis of series of 2-[4-(2-amino-6-phenyl-6*H*-1,3-thiazin-4-yl)phenoxy]ethanol derivatives from 1-[4-(2-hydroxyethoxy)phenyl]-3-phenylprop-2-en-1-one with thiourea in presence ethanolic sodium hydroxide then characterization and *in-vitro* evaluation of antimicrobial activity. All synthesized compound showed comparable activity.

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