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SYNTHESIS CHARACTERIZATION AND BIOLOGICAL STUDY OF THIAZINE

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ABSTRACT

A series of novel 2-[2-Amino-6-(4-substitutedphenyl)-6H-1,3-thiazin-4-yl]-4-tert-butyl-3-substitutedphenol were synthesized from different substituted 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl)-3-(4-substituted phenyl) prop-2-en-1-one and thiourea were dissolved in ethanolic potassium hydroxide solution and stirred for 5-6 hours. The structures of the compounds were elucidated by elemental and spectral (IR, ^1H NMR,) analysis. The synthesized compounds were checked for biological evaluation i.e. Antimicrobial, Antifungal, Study Antioxidant Activity.

Keywords : *chalcone, Thiazines, biological evaluation, antimicrobial, antifungal study Antioxidant Activity.*

INTRODUCTION

Nitrogen and sulphur based heterocyclic molecules have gained significant attention owing to their broad spectrum pharmacological profiles. Thiazine is one of such promising scaffolds which have been widely utilized in the synthesis of compounds that possess interesting biological profileNow a day's heterocyclic compounds analogues and derivatives have become strong interest in pharmaceutical research area because of their useful biological and pharmacological properties. Heterocyclic compounds are abundant in nature and have acquired more importance because their structural subunits are exhibit in many natural products such as vitamins, hormones, antibiotics etc. Thiazines are organic compounds with

molecular formula C4H5NS. Thiazine is a six member heterocyclic ring system, which contains two heteroatoms (N & S) placed in the heterocyclic ring.

Materials& Methods

Step I –

Synthesis of 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl) ethan-1-one (1-2)

General Procedure:- In hot glacial acetic acid, fused zinc chloride was added and refluxed till solid was dissolved. Then powdered 4-tert-butyl-3-substituted phenol was added and refluxed for
eight hours. The reaction mixture was cooled and then poured in acidulated water. The solid obtained was filtered, washed with water and recrystallized from rectified spirit to obtain 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl) ethan-1-ones.

Step II –

Synthesis of 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl)-3-(4-substituted phenyl) prop-2-en-1-one (3a-f)

In ethanol solvent, 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl) ethan-1-one and aromatic aldehyde were added. To this mixture, dropwise added 10 % of KOH solution with constant stirring. The reaction mixture was kept overnight. Then this mixture was poured over crushed ice. The product 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl)-3-(4-substitutedphenyl) prop-2-en-1-one was filtered and recrystallized from ethanol .

Step III –

SYNTHESIS OF THIAZINE DERIVATIVES (5a-f)

An equimolar quantity of 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl)-3-(4-substituted phenyl) prop-2-en-1-one andthiourea were dissolved in ethanolic potassium hydroxide solution and stirred for 5-6 hours. This was then poured into cold dilute hydrochloric acid solution with continuous stirring for an hour and kept in refrigerator for overnight and the precipitate obtained was filtered and dried. It was then recrystalized using petroleum ether to get titled compounds

Result & discussion:

Scheme

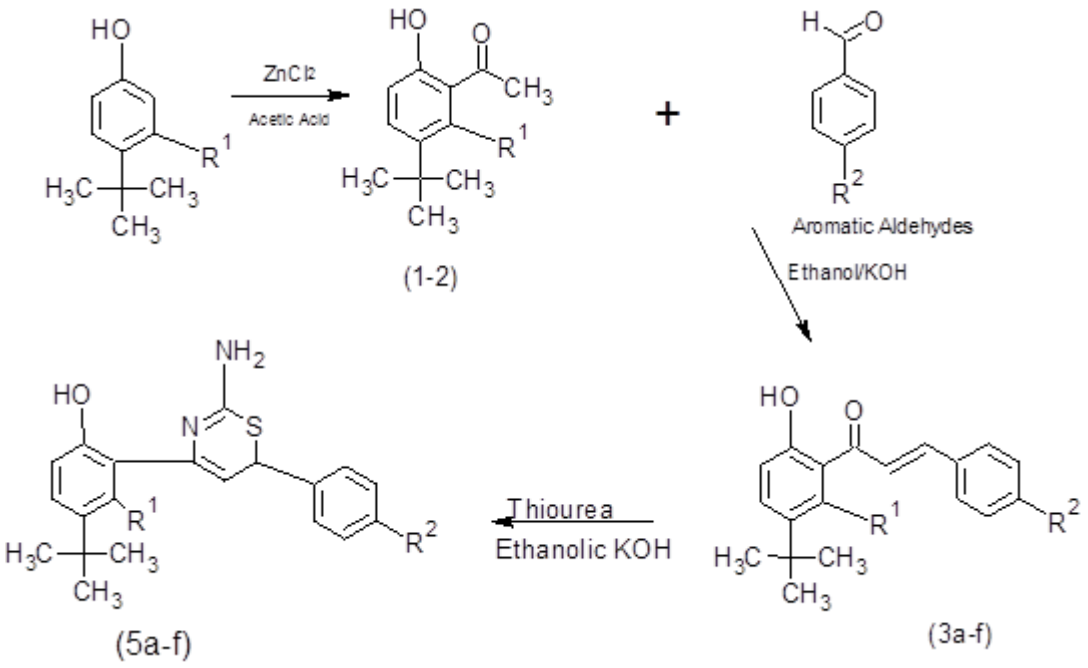

Table1: Physical property of compounds

Compounds	R1	R2	Molecular Formula	MP◦C	%Yield	R.F. Value	% Nitrogen	
							Found	Calculated
5a	Cl	Cl	$C_{20}H_{20}ON_2SCl_2$	129	41%	0.62	6.84	6.88
5b	Cl	Br	$C_{20}H_{20}ON_2SClBr$	135	38%	0.52	6.70	6.73
5c	Cl	OH	$C_{20}H_{21}O_2N_2SCl$	139	45%	0.56	7.00	7.2
5d	Br	Cl	$C_{20}H_{20}ON_2SClBr$	155	42%	0.59	6.00	6.2
5e	Br	Br	$C_{20}H_{20}ON_2SBr_2$	142	52%	0.48	5.61	5.65
5f	Br	OH	$C_{20}H_{21}O_2N_2SBr$	152	36%	0.68	6.42	6.47

Spectral Analysis (Compound No. 5b):

IR analysis (wave number in cm^{-1}) : 3100-3000 cm^{-1} (Ar-H stret.), 3200-3300 (-OH stret), 3200-3250 (-NH_2 stret.), 700-720 (C-Cl stret.), 500-550 (C-Br stret), 1675-1517(N-H stret), 1250-1270(C-S-C stret)

NMR analysis (δ ppm): 1.35 (-CH_3, 9H), 7.56 (-NH_2, 2H), 8.35 (-OH,1H), 4.50 (Ha), 6.5- 8 (Ar-H , 7H)

BIOLOGICAL STYDY: Antimicrobial and antifungal activity

Table 2: Antimicrobial activity

Sr. No.	Compounds	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus Aureus*	*Bacillus subtilis*
1	5a	17	18	16	17
2	5b	12	17	14	15
3	5c	15	16	18	17
4	5d	13	10	12	17
5	5e	11	16	13	07
6	5f	18	16	12	09

Table 3: antifungal activity

Sr. No	Name of Compound	**Antifungal Activity**	
		A. Niger	C.albicans
1	5a	17	15
2	5b	16	14
3	5c	16	17
4	5d	12	14
5	5e	13	09
6	5f	17	10

The antimicrobial and antifungal activity of all newly synthesized compounds was evaluated against gram-negative *Escherichia coli, Pseudomonas aeruginosa,* and gram-positive bacteria *Staphylococcusaureus, Bacillus subtilis.*The culture of each microbes species was incubated at 37 ^{o}c and the zone of inhibition on agar plates (diffusion method) was measured after 24 hrs. Most of these compounds were found active.

Antioxidant Activity: Total phenolic content

Total phenolic content was determined as described by Prior et al. [21]. Briefly, 500 µg of compound in 100 µL of methanol was mixed with 100 µL of 1 N Folin–Ciocalteu reagent. Following incubation for 5 min, 200 µL of 20% Na_2CO_3 was added. Absorbance at 730 nm was measured in plate reader after 10 min and the concentration of phenolic compounds was calculated using standard curve of gallic acid (500–5000 ng; R^2=0.967). The results were expressed as mg gallic acid equivalent (mg GAE) g^{-1} .

Thiazine derivatives :

Table No. 4 :

Sr.No	Sample	µgGAE/mg
1	2-[2-Amino-6-(4-chlorophenyl)-6*H*-1,3-thiazin-4-yl]-4-*tert*-butyl-3-chlorophenol	17
2	2-[2-Amino-6-(4-bromophenyl)-6*H*-1,3-thiazin-4-yl]-4-*tert*-butyl-3-chlorophenol	13
3	2-[2-Amino-6-(4-hydroxyphenyl)-6*H*-1,3-thiazin-4-yl]-4-*tert*-butyl-3-chlorophenol	16
4	2-[2-Amino-6-(4-chlorophenyl)-6*H*-1,3-thiazin-4-yl]-4-*tert*-butyl-3-bromophenol	18
5	2-[2-Amino-6-(4-bromophenyl)-6*H*-1,3-thiazin-4-yl]-4-*tert*-butyl-3-bromophenol	21
6	2-[2-Amino-6-(4-hydroxyphenyl)-6*H*-1,3-thiazin-4-yl]-4-*tert*-butyl-3-bromophenol	26

Above synthesized 2-[2-Amino-6-(4-substitutedphenyl)-6H-1,3-thiazin-4-yl]-4-tert-butyl-3-substitutedphenol derivative (Table No. 2,3 and 4) shows good Antimicrobial, Antifungal, Study and Antioxidant Activity.

On the basis of screening data it was observed that these heterocyclic compounds can be easily used against treatment of disease caused by test microbes.

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