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SYNTHESIS CHARACTERIZATION AND BIOLOGICAL STUDY OF ISOXAZOLINE

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ABSTRACT

A series of novel 4-tert-butyl-3-substituted-2-[5-(4- substituted phenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenolwere synthesized from different substituted 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl)-3-(4-substituted phenyl) prop-2-en-1-one.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 activity and Antioxidant Activity.

Keywords: *chalcone, isoxazoline, biological evaluation, antimicrobial, antifungal study.*

INTRODUCTION

Isoxazoline are biologically active, synthetically useful, and important heterocycles having a wide role in medicinal chemistry. It is widely used as an antibacterial, anti-inflammatory, antifungal agent. Isoxazolines are also reported to possess good antimicrobial, analgesic, anti-inflammatory activity. In view of the biological activities, some isoxazoline derivatives and in continuation of our research work on synthesis of biologically active heterocyclic compounds, we investigated that the synthesis of some novel isoxazoline derivatives from

chalconised derivatives is synthesized .The structure of all compounds was established on the basis of spectral and elemental analysis.

Materials& Methods

Step I –

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

General Method :

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 titled compound. Thus 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl) ethan-1-ones were synthesized

Step II –

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

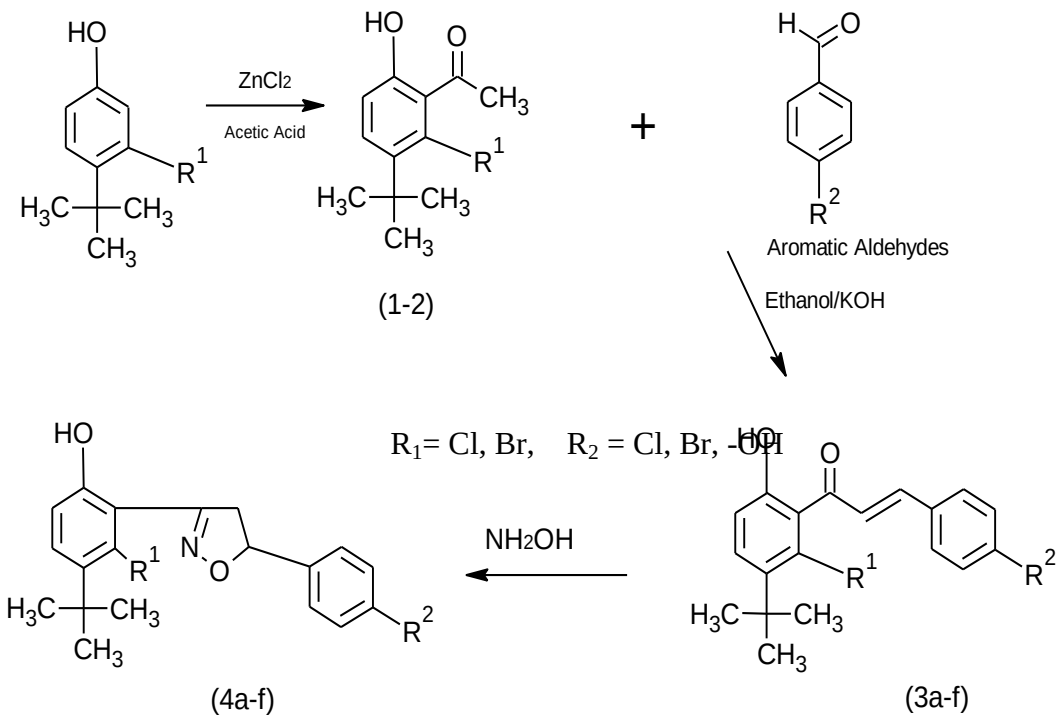
In ethanol solvent, 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl) ethan-1-one and aromatic aldehyde were added . To this mixture, dropwise added 10 % of KOH solution with constant stirring. The reaction mixture was kept overnight. Then this mixture was poured over HCland crushed ice. The product 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl)-3-(4-substitutedphe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

Step III -Synthesis of Isoxazolinederivatives (4a-f)

An equimolar quantity of 1-(3-tert-butyl-2-substituted-6-hydroxyphenyl)-3-(4-substituted phenyl) prop-2-en-1-one, hydroxylamine hydrochloride andsodium acetate in ethanol solvent was refluxed for about 6hours. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized to get substituted isoxazolines.

Result &discussion:

Scheme



The present protocol for the synthesis of starting chalcones was done by using literature procedure, in which 4-substitudedaldehyde was mixture with 4-tert-butyl-3-substituted phenol in ethanol absolute and sodium hydroxide 10% to produce compound 3a-fThe different chalcones shows different product yield. As per literature, number ofthe procedure are available to carry out the reaction with different experiential condition but product utility of these product for different pathological and pharmaceutical in great importance.Finally 3a-f reacts with $NH_2OH$to give substituted isoxazolines.

Table1: Physical property of compounds

Compounds	R1	R2	Molecular Formula	MP◦C	%Yield	R.F. Value	% Nitrogen	
							Found	Calculated
4a	Cl	Cl	$C_{19}H_{19}O_2NCl_2$	202	48%	0.41	3.83	3.85
4b	Cl	Br	$C_{19}H_{19}O_2NClBr$	235	58%	0.47	3.41	3.43
4c	Cl	OH	$C_{19}H_{20}O_3NCl$	199	49%	0.52	4.03	4.05
4d	Br	Cl	$C_{19}H_{19}O_2NClBr$	192	42%	0.57	3.43	3.43
4e	Br	Br	$C_{19}H_{19}O_2NBr_2$	240	57%	0.62	3.08	3.09
4f	Br	OH	$C_{19}H_{20}O_3NBr$	175	42%	0.60	3.58	3.59

Spectral Analysis (Compound No. 4e):

IR analysis (wave number in cm^{-1}) 3100-3000 (Ar-H stret.), 3100-300 (CH_3 stret.), 500-550 (C-Br stret.), 700-720 (C-Cl stret.), 3200-3300(-OH)

NMR analysis (δ ppm): 6.5-8 (Ar-H, 6H),8.93 (Ha),3.85-3.60 (Hb), 8.37(-OH,1H),1.5(-CH_3, 9H**)**

BIOLOGICAL STYDY

Antimicrobial and antifungal activity

Table 1: Antimicrobial activity

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

Table2:Antifungal activity

Sr. No.	Compounds	Antifungal Activity	
		A. Niger	B. Albicans
1	4a	18	17
2	4b	12	16
3	4c	17	18
4	4d	15	12
5	4e	13	11
6	4f	14	07

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.

The antimicrobial and antifungal screening (Table-1 and 2) of above synthesized4-tert-butyl-3-substituted-2-[5-(4- substituted phenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenol shows good activity against all microbes species. 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.

Isoxazole derivatives :

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} .

Pyrimidine derivatives :

Sr.No	Sample	µgGAE/mg
1	4-*tert*-butyl-3-chloro-2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenol	19
2	4-*tert*-butyl-3-chloro-2-[5-(4-bromophenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenol	09
3	4-*tert*-butyl-3-chloro-2-[5-(4-hydroxyphenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenol	12
4	4-*tert*-butyl-3-bromo-2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenol	15
5	4-*tert*-butyl-3-bromo-2-[5-(4-bromophenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenol	17
6	4-*tert*-butyl-3-bromo-2-[5-(4-hydroxyphenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenol	18

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