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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 2-(SUBSTITUTED PHENYL CARBOXAMIDO)-4-(O-ETHYLACETATE OXY PHENYL) THIAZOLE DERIVATIVES

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ABSTRACT

A new series of compounds derived from 2-(substituted phenyl carboxamido) -4 - (o-ethylacetate oxy phenyl) thiazole derivatives were screened and the structures of these compounds were confirmed by IR, ^{1}H NMR spectral data and CHN analysis. These compounds were evaluated for antimicrobial activities; some of these compounds have shown good antibacterial and antifungal activity.

Key words : Thiazoles, Antimicrobial activity

INTRODUCTION

The presence of oxygen and sulfur in the heterocyclic system has attracted the attention of medicinal chemists because of the diverse biological activities and profound efficacy. Morever, much interest has been focused on biological activities of thiazole derivatives[1].The recent review of literature have highlighted that, 2, 3-dihydroimidazo [2, 1-b] thiazole-5-carboxamides[2], 2-[(benzazol-2-yl) thioacetyl amino] thiazoles[3], 4-(5-nitro-2-furyl / 2-pyrizinyl / 1-adamantyl)-2-9alkyl / aryl / arylamino) thiazoles[4] and some new 2, 4-disubstituted thiazoles[5] have been reported to exhibit significant antibacterial, antifungal, antitubercular, analgesic and anti-inflammatory activities. In view of this, synthesis of 2-(substituted phenyl carboxamido)-4-(o-ethylacetate oxy phenyl) thiazole derivatives has been undertaken in the present investigation. The intermediate ethyl [o-(2-amino-4-

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thiazolyl)] phenoxyacetate (III) was condensed with substituted aromatic acid chloride (prepared by reaction of substituted aromatic acid with thionyl chloride) in presence of pyridine and hydrochloric acid leading to formation of 2-(substituted phenyl carboxamido)-4-(o-ethylacetate oxy phenyl) thiazole derivatives **(IVa-g)** in good yield **(Scheme 1)**. The structures of these derivatives were assigned on the basis of CHN analysis and spectral data. The compounds were screened for antimicrobial activity.

EXPERIMENTAL

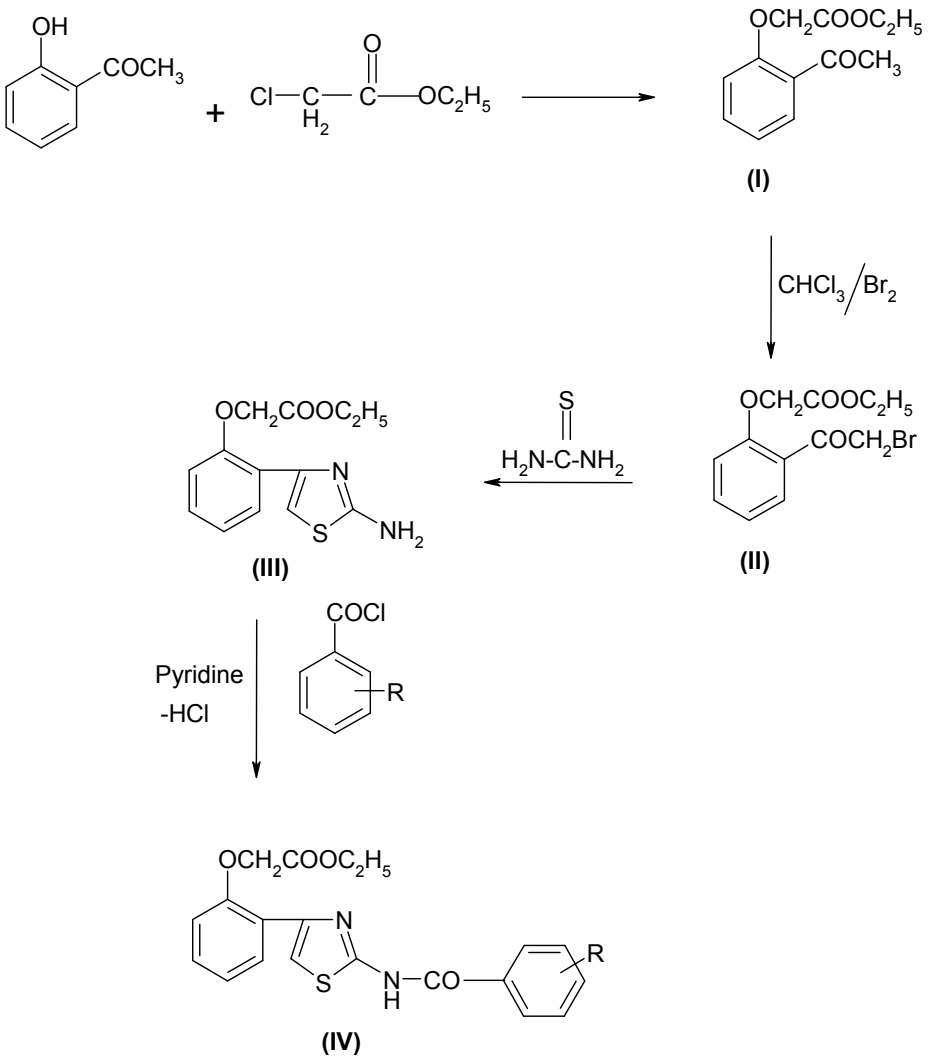
All the melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded in KBr on a Shimadzu 8700 FTIR spectrophotometer. Purity of the compounds was checked on silica gel TLC plates. ^{1}H NMR (400 MHz) spectra were recorded on a Perkin Elmer- 32 NMR spectrometer using TMS as internal standard and $CDCl_3$ as a solvent. Thermo Finnigan FLASH EA1112 CHNS elemental analyzer was used to determine the percentages of C, H and N.

Preparation of ethyl –o-acetoxyl- phenoxy acetate (I)

To a mixture of o-hydroxyacetophenone (6.8 mL, 0.05M) and ethyl chloroacetate (6.1 mL, 0.05M). The solution of sodium hydroxide (100 mL, 0.45M) was added, followed by stirring to room temprature. The solvent was evaporated and to the resulting reaction mixture, 150 mL of water was added followed by acidification with HCl (5M). The resulting solid was filtered, dried and recrystallized from ethanol. Purity of the compound was checked by TLC using cyclohexane : ethyl acetate (6 : 4) as mobile phase, **(I).** IR (KBr) cm^{-1} : 2911.99 (C-H ali), 1704.8 (C-O-C), 1644.98 (C=O str), 1596.8 (C=C str).

Preparation of ethyl (o-bromoacetyl) phenoxyacetate (II)

A mixture of ethyl-o-acetoxyl-phenoxyacetate (10 g, 0.045M) and chloroform (25 mL) was slightly warmed. The reaction mixture was stirred on a magnetic stirrer, simultaneously bromine was added dropwise. Stirring was continued for 2 hrs at room temperature. The chloroform layer was evaporated. The residue obtained was digested with sodium bicarbonate solution. The resulting solid was filtered, washed with cold water, dried and recrystallized from ethanol. Purity of the compound was checked by TLC using cyclohexane : ethylacetate (6 : 4) as mobile phase **(II).** IR (KBr) cm^{-1} : 3037.4 (C-H ar), 2921.6 (C-H ali), 1754.9 (C-O-C), 1681.6 (C=O str), 1598.7 (C=C str), 619 (C-Br).



R= H, 4-NO_2, 4-OCH_3, 4-Cl, 2-Cl, 4-CH_3, 3-CH_3

Scheme 1

Preparation of ethyl [o-(2-amino-4 thiazolyl)] phenoxyacetate (III)

A mixture of ethyl (o-bromoacetyl)-phenoxyacetate **(II)** (2 g, 1M) and thiourea (3 g, 1.5 mL) was dissolved in 20 mL of ethanol. The reaction mixture was refluxed for 90 min. It was then cooled and poured into 40 mL cold water. Being highly acidic, the

reaction mixture was neutralized with anhydrous potassium carbonate to obtain the white solid. The solid was separated, filtered, washed with cold water, dried and recrystallized from ethanol to give **(III).** IR (KBr) cm^{-1} : 3713.77, 3309.2 (NH_2 str), 3161.1 (C-H ar), 2979.8 (C-H ali), 1728.1 (C-O-C), 1512.09 (C-N str), ^1H NMR ($CDCl_3$) : δ 8.11 (d, 1H, Ar-H), 7.66 (s, 1H, Ar-H), 6.7-7.2 (m, 3H, Ar-H), 5.12 (s, 2H, NH_2), 4.20-4.70 (m, 7H, -CH_2-CH_2-CH_3).

General procedure for preparation of 2-(substituted phenyl carboxamido)-4-(o-ethyl acetate oxy phenyl) thiazole (IV)

A mixture of ethyl [o-(2-amino-4 thiazolyl)] phenoxyacetate (1 g, 0.02 mL) in pyridine (25 mL) was added to substituted aromatic acid chloride (1 g, 0.02 mL). It was then stirred for 1 hr and the contents were poured into 500 mL ice cold water. The solid thus separated was filtered, washed with cold water, dried and recrystallized from ethanol. The characterization data of 2-(substituted phenyl carboxamido) - 4 -(o-ethyl acetate oxy phenyl) thiazole derivatives are recorded in Table 1.

Table 1. Characterization data of the compounds (IVa-g)

Compd.	R	Mol. formula	Mol. wt.	Yield (%)	M. P. (^oC)	R_f Values
IVa	H	$C_{20}H1_8O_4N_2S$	382	73.21	100-102	0.32
IVb	4-NO_2	$C_{20}H_{17}O_6N_3S$	427	76.00	94-96	0.72
IVc	4-OCH_3	$C_{21}H_{20}O_5N_2S$	412	72.83	238-240	0.34
IVd	4-Cl	$C_{20}H_{17}O_4N_2SCl$	416	66.67	154-156	0.56
IVe	2-Cl	$C_{20}H_{17}O_4N_2SCl$	416	70.57	98-100	0.34
IVf	4-CH_3	$C_{21}H_{20}O_4N_2S$	396	68.59	78-80	0.28
IVg	3-CH_3	$C_{20}H_{18}O_4N_2S$	396	78.88	46-48	0.36

Compounds **IVa-g**. Recrystallized from ethanol.

Antimicrobial activity

The synthesized compounds (**IVa-g**) have been evaluated for their antimicrobial activity[6-8]. Agar diffusion method was used for assessing antibacterical activity against *Staphylococcus aureus, Bacillus subtilis* Gram positive and *Escherichia coli, Klebsiella*

pneumoniae Gram negative bacteria and antifungal activity against *Candida albicans* and *Aspergillus niger*. The sterilized agar medium was poured into petri dishes and allowed to solidify. On the surface of the media, microbial suspension was spread over the agar plates to solidify. All the synthesized compounds (100 µg/mL) in DMSO were placed serially in the cavities, with the help of micropipette. The plates were incubated at 37ºC for 24-48 hrs. After incubation, the diameter of growth inhibition zone was measured in mm. Under similar conditions, controlled experiment was carried out by using amoxycillin and amphotericin as standard drug for comparison, respectively. The results are recorded in Table 2.

Table 2. Antimicrobial evaluation data of the compounds (IVa-g)

Compound	Antibacterial in (µg/mL)				Antifungal in (µg/mL)	
	S. a.	**B. s.**	**E. c.**	**K. p.**	**C. a.**	**A. n.**
IVa	12	11	nil	09	09	12
IVb	14	20	12	20	08	16
IVc	nil	17	06	Nil	12	11
IVd	10	16	13	20	15	16
IVe	07	12	14	09	nil	10
IVf	08	12	nil	07	06	08
IVg	11	08	15	nil	10	Nil
Amoxycillin	25	27	23	28	-	-
Amphotericine	-	-	-	-	19	18

S. a : S. aureus B. s : B. subtilus E. c : E. coli K. P. : K. Pneumoniea
C. a : C. albicans A. n : A. niger

RESULTS AND DISCUSSION

By visualizing evaluation data of newly synthesized compounds **(IVa-g)**, in antibacterial screening, it was observed that compounds (**IVb)** and (**IVd)** showed good activity against *K. pnuemoniae* and *B. subtilis*. Compound (**IVc)** and (**IVe)** showed good activity against *E. coli* and *S. aureus,* respectively. Amogst all compounds (**IVb)** exhibited

good activity against all strains of bacteria. While remaining compounds showed less activity or inactive against *S. aureus, B. subtilis, E. coli and K. pneumoniae.* In antifungal screening, it is observed that compounds (**IVb)** and (**IVd)** showed good activity against *A. niger*. Compounds (**IVd)** and (**IVc)** showed good activity against *C. albicans* and compound (**IVa)** exhibited good activity against *A. niger*. Amongst all compounds (**IVd)** exhibited good activity against all strains of fungi, while remaining compounds showed less activity or inactive against *C. albicans* and *A. niger*. The results obtained validate the hypothesis that the 4-chloro and 4-nitro substitution in the aromatic ring has good role in antibacterial as well as antifungal activity. Future modifications of compounds (**IVa-g)** may lead to a new generation of inhibitors.

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