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Synthesis and Evaluation of Antimicrobial Activity of some Sulfur Nitrogen contain Heterocycles

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Abstract

The structural and therapeutic diversity coupled with commercial viability of small heterocyclic molecules has fascinated organic and medicinal chemists. So, a great deal of research is carried out in the field of heterocycles containing sulfur and nitrogen, because of their immense biological importance.Research in field of antimicrobial therapy is continuous ongoing & demanding study. Among the several reasons the major ones are the resistance developed by microbes and the emergence and occurrence of newer infections. Hence the search for newer effective antimicrobial agents is imperative. It focuses on the problems of cross resistance & better activity against variety of infections.The main focus of this research work was to synthesize, purify and characterize the thiazole analogs and return for their antimicrobial and antifungal activity. Most of the compounds synthesized showed good antibacterial activity within the series against both Gram - ve and Gram + ve bacteria at 100 µg/0.1 ml concentration.

Keywords: Hetrocycles, Antimicrobial, Nitrogen

Introduction

In the field of science and technology, medicinal chemistry has been a fascinating subject. The rapid development in the last seven decades has been truly a challenging and very exciting. Medicinal chemistry according to Burger, "***tries to be based on the ever-increasing hope that biochemical rationales for drug discovery may be found***". Medicinal chemistry is the branch of science, which has remarkable value for synthesis of novel drugs with intense therapeutic activity. It concerns with discovery, development, identification and interpretation of mode of action of biologically active compounds at molecular level. The molecular biological revolution and progressive mapping of human 'genome' have created a new biochemical and bio structural 'world order. Five membered heterocyclic compounds with an additional 'N' heteroatom are termed azoles. Thiazoles are the five membered ring systems with two hetero atoms (S and N) placed in the heterocyclic ring at 1, 3- positions. Thiazoles are structurally related to thiophene and pyridine but in most of its properties it resembles the latter.The thiazole ring has been extensively studied and it forms a part of Vitamin B_1, Penicillins and the antibacterial thiazoles. Reduced thiazoles serve in the study of polypeptides and proteins and occur as structural units in compounds of biological importance.

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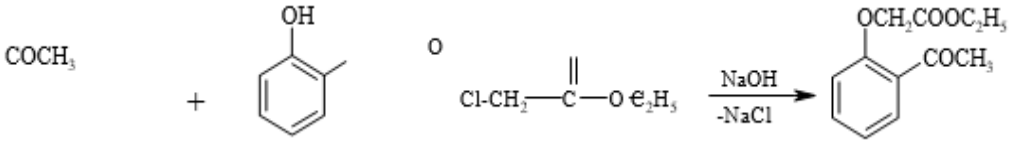
Material and Methods

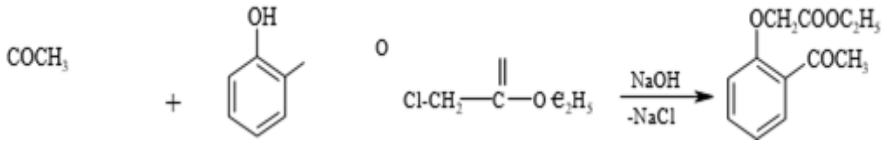
Ethyl-*o*-acetoxyl-phenoxyacetate (I)



Chemicals	Quantity	Molar quantity
o-Hydroxyacetophenone	6.8 ml	0.05 M
Ethyl cholroacetate	6.1 ml	0.05 M
NaOH	4.5 g	0.45 M

A mixture of *o*-hydroxyacetophenone (6.8ml, 0.05M), ethyl chloroacetate (6.1ml, 0.05M) was taken to this a solution of sodium hydroxide (100ml, 0.45M) was added dropwise with stirring, the solvent was evaporated. To the residue150ml of water was added, acidified with hydrochloric acid (5M). Filtered the precipitate under reduced pressure to get a white solid.

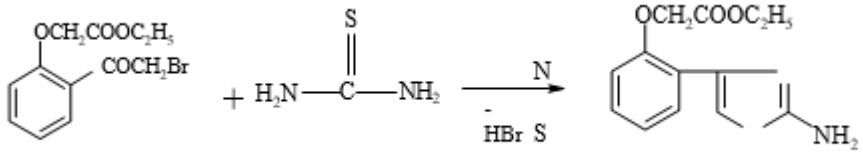
Ethyl-(*o*-bromoacetyl) phenoxyacetate(II)



Chemicals	Quantity	Molar quantity
Ethyl-*o*-acetoxyl-phenoxyacetate	2 g	0.01M
Bromine	0.5 ml	0.01M
Chloroform	25ml	

Ethyl-*o*-acetoxyl-phenoxyacetate (10g, 0.045mol) and chloroform (25ml) were taken in a beaker & warmed slightly; the mixture was stirred continuously on a magnetic stirrer, simultaneously added bromine dropwise (from dropping funnel). It was then stirred for 2 hr, at room temperature. Evaporated the chloroform layer. The residue obtained was digested with sodium bicarbonate solution. The precipitate obtained was filtered, washed with water and recrystallized from ethanol.

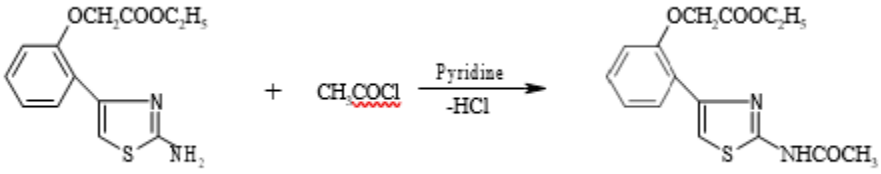
Ethyl[*o*-(2-amino-4-thiazolyl)] phenoxyacetate(III)



Chemicals	Quantity	Molar Quantity
Ethyl-(*o*-bromoacetyl) phenoxyacetate	2.0g	1.0 M
Thiourea	3.0g	1.5 M
Alcohol	20ml	

Ethyl (*o*-bromoacetyl)-phenoxyacetate (2g,1mol) and thiourea (3g, 1.5mol) were taken and dissolved in 20 ml of ethanol in 100ml round bottom flask and was refluxed for 90 min. The reaction mixture was cooled and poured into 40ml water. Being highly acidic, the mixture was neutralized with anhydrous potassium carbonate to obtain the white solid.

Preparation of 2-acetyl caboxymido-4-(*o*-ethyl acetate oxy phenyl) thiazole

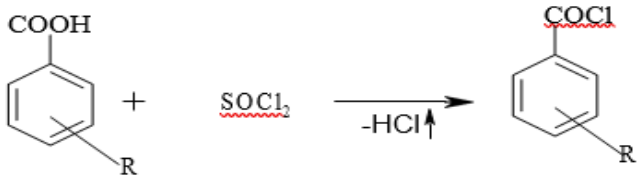


Chemicals	Quantity	Molar Quantity
Ethyl[*o*-(2-amino-4-thiazolyl)]phenoxyacetate	1.0 g	0.0035M
Acetyl chloride	1.56 ml	0.02M
Pyridine	25.0 ml	0.0054M

Preparation of acetyl derivative:-

Ethyl[*o*-(2-amino-4-thiazolyl)] phenoxyacetate(1g, 0.0035mol) was taken in 25ml of pyridine. acetyl chloride (1.56ml,0.02mol) was added and stirred it for 1 hr. The reaction mixture was poured into 500ml ice cold water, precipitate obtained was filtered and recrystallized with ethanol.

General Procedure for preparation of substituted aromatic acid chloride: -

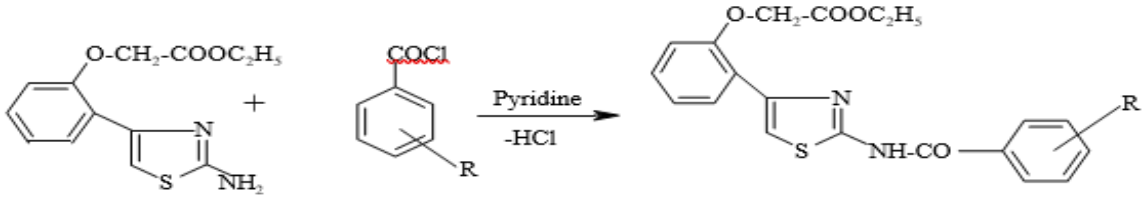
An 

equimolar proportion of thionyl chloride and aromatic acid (0.1M) was taken in a 500 ml round bottom flask and refluxed for 90 minutes. The excess of thionyl chloride was by distilled off to get the corresponding acid chloride.

Table No.

Comp. code	R
GKRS-2	H
GKRS-3	4-NO_2
GKRS-4	4-OCH_3
GKRS-5	4-Cl
GKRS-6	2-Cl
GKRS-7	4-CH_3
GKRS-8	3-CH_3

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



Ethyl[*o*-(2-amino-4-thiazolyl)] phenoxyacetate (1g,0.02mol) was taken in 25 ml pyridine. To this acid chloride (1g, 0.02mol) was added and stirred it for 1 hr. The reaction mixture was poured into 500 ml ice cold water. Precipitate obtained was filtered and recrystallized by ethanol.
TLC System:- Cyclohexane : Ethyl Acetate

The charectorisation data of carboxamide derivatives of Ethyl[*o*-(2-amino-4-thiazolyl)] phenoxyacetate is presented in Table

Table .: List of 2(substituted phenyl carboxamido)-4-(*o*-ethyl acetate oxy phenyl) thiazole with their charectorisation data.

Comp. code	R	Mol. Form.	Mol. Wt.	% Yield	Recryst. Solvent	M.P. (^{0}C)	R_f
GKRS-2	H	$C_{20}H_{18}O_4N_2S$	382	73.21	Ethanol	100-102	0.32
GKRS-3	4-NO_2	$C_{20}H_{17}O_6N_3S$	427	76.00	Ethanol	94-96	0.72
GKRS-4	4-OCH_3	$C_{21}H_{20}O_5N_2S$	412	72.83	Ethanol	238-240	0.34
GKRS-5	4-Cl	$C_{20}H_{17}O_4N_2SCl$	416	66.67	Ethanol	154-156	0.56
GKRS-6	2-Cl	$C_{20}H_{17}O_4N_2SCl$	416	70.57	Ethanol	98-100	0.34
GKRS-7	4-CH_3	$C_{21}H_{20}O_4N_2S$	396	68.59	Ethanol	78-80	0.28
GKRS-8	3-CH_3	$C_{20}H_{18}O_4N_2S$	396	78.88	Ethanol	46-48	0.36

Analytical Techniques

Physical data

Melting points of the synthesized compounds were determined using Thiele's melting point apparatus and were found uncorrected.

Thin Layer Chromatography (TLC)

Purity of the compounds was checked by thin layer chromatography using silica gel G as stationary phase and various combinations of ethyl acetate: cyclohexane, as mobile phase. The spots resolved were visualized as brown coloured spots by using iodine chamber.

Instrumentation

The techniques employed for the characterization of the synthesized compounds were UV spectra, IR spectra, ^{1}H-NMR spectra and elemental analysis.

UV spectra

The UV spectra of the synthesized compounds were recorded on UV – Visible spectrophotometer (Shimadzu-1601, Al-Ameen College of Pharmacy, Bangalore) and the wave length were recorded in nm. Absorbance was taken at the max characteristic for each compound.

Infrared spectra

The IR spectra of the synthesized compounds were recorded using KBr pellets in range of 4000-400cm^{-1} on a Fourier transform IR spectrometer (model shimadzu 8700, Al-Ameen College of Pharmacy, Bangalore) and IR spectrometer (IISc, Bangalore) and the frequencies were recorded in wave numbers.

^{1}H – NMR magnetic resonance spectra

^{1}H – NMR (400 mhz) spectra were recorded in chloroform –d in Amx – 400 liquid state NMR spectrometer (Indian Institute of Science, Bangalore). Chemical shifts (δ) are reported in parts per million downfield from internal reference Tetramethyl Silane (TMS).

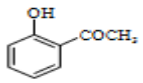
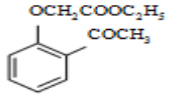
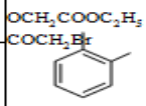
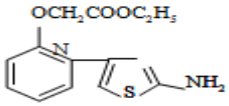
Elemental Analysis

Elemental analysis was performed and the reports were obtained on Thermo Finnigan FLASH EA

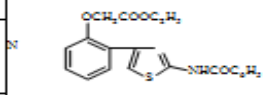
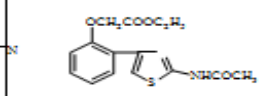
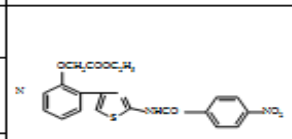
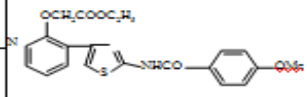
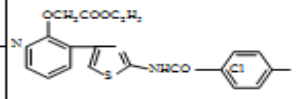
1112 CHNS analyzer, Dept. of Organic Chemistry, IISc, Bangalore.

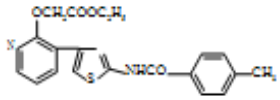
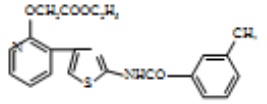
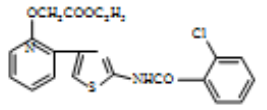
Results and Discussion

SYNTHETIC WORK

Spectrum	Structure	Characteristics
UV (λ_{max})		262 nm
UV (λ_{max})		303 nm
IR (γ_{max})		2911.99 (C-H Ali), 1704.8 (C-O-C), 1644.98 (C=O str), 1596.8 (C=C str), 1260-1000 (C-O str).
UV (λ_{max})		275 nm
IR (γ_{max})		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).
UV (λ_{max})		300 nm
IR (γ_{max})		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), 1280-1000 (C-O str).
NMR		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).

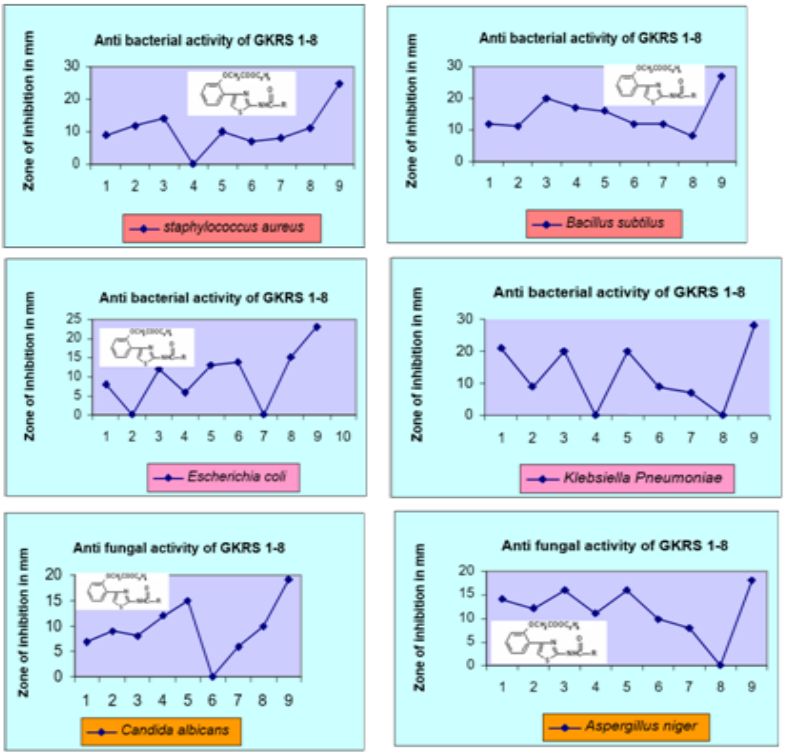
ISSN: 0976-7126
Soni *et al.*, 12(9):11-34, 2021

UV (λ_{max})		261 nm
IR (ν_{max})		3471.6 (N-H str), 3062.8 (Ar C-H), 2979.8 (C-H Ali), 1751.3 (C=O, Ester), 1664.5 (C=O str), 1536.2 (C-N str), 1280-1000 (C-O str).
NMR		3.68-4.99(m, 7H, -CH_2 –CH_2 –CH_2), 6.77-8.08(m, 11H, Ar-H-NH-CO)
UV (λ_{max})		275 nm
IR (ν_{max})		3083.9 (C-H Ar), 2977.9 (C-H Ali), 1755.1 (C=O Ester), 1654.8 (C=O str), 1560.3 (C=C str).
UV (λ_{max})		263 nm
IR (ν_{max})		3334.7 (N-H str), 3076.25(C-H Ar), 2993.3 (C-H Ali), 1720.4 (C=O Ester), 1666.4 (C=O str), 1527.5 (N=O str).
CHN Analysis		% C H N Calculated 56.2 4.01 9.83 Found 54.8 4.41 9.56
UV (λ_{max})		263 nm
IR (ν_{max})		3334.7 (N-H str), 3076.25(C-H Ar), 2993.3 (C-H Ali), 1720.4 1681.8 (C=O str), 1595 (C=C str).
UV (λ_{max})		266 nm
IR (ν_{max})		3267.2 (NH str), 3076.3 (C-H Ar), 2935.5 (C-H Ali), 1722.3 (C=O Ester), 1666.4 (C=O str), 1604.7 (C=C str), 1200-1000 (C-Cl)

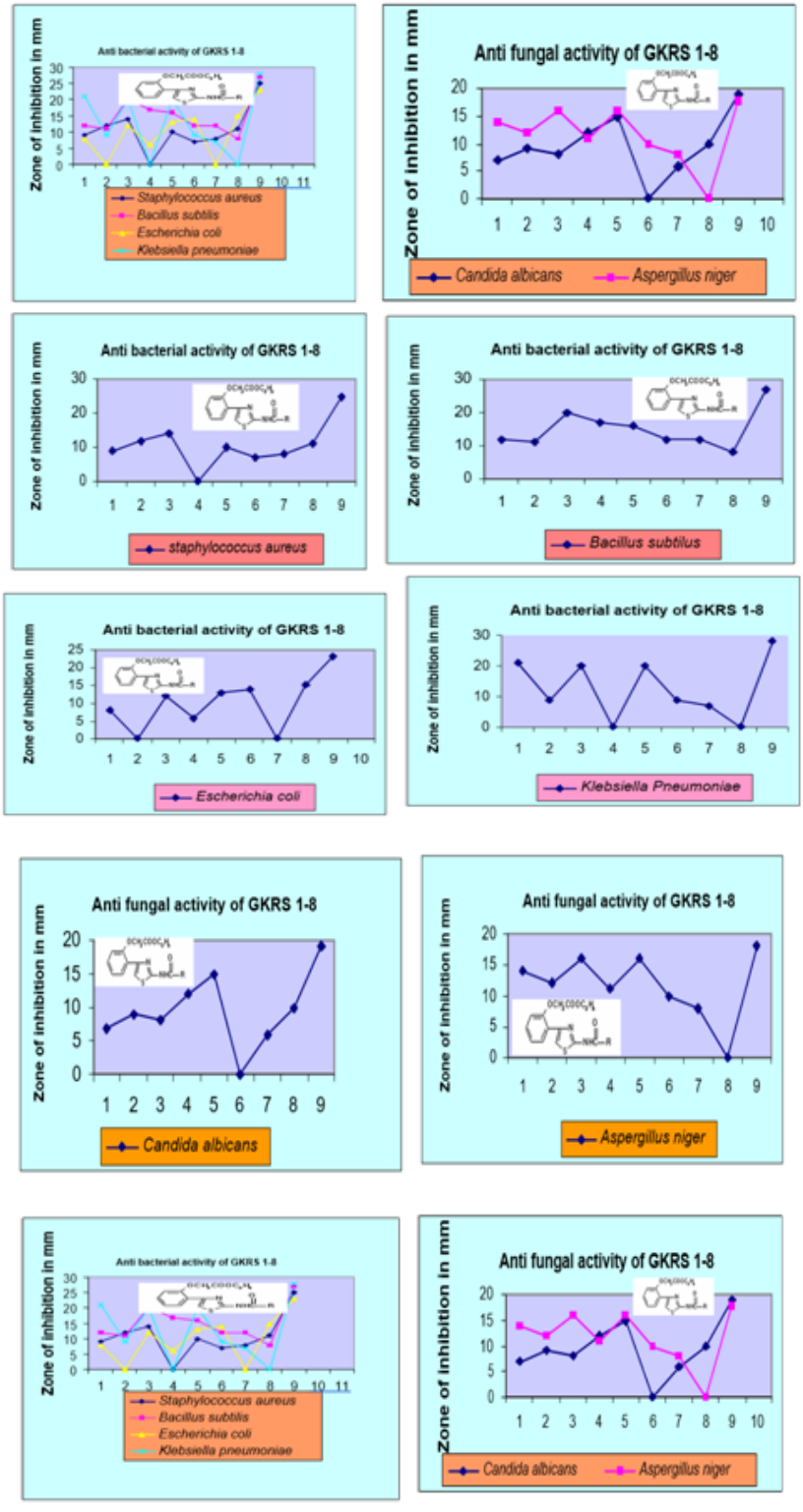
UV (λ_{max})		263 nm
IR (ν_{max})		3334.7 (N-H str), 3076.25(C-H Ar), 2993.3 (C-H Ali), 1720.4, 1712.7 (C=O Ester), 1608.5 (C=C str), 1250-1000 (C-O).
UV (λ_{max})		260 nm
IR (ν_{max})		3334.7 (N-H str), 3076.25(C-H Ar), 2993.3 (C-H Ali), 1720.4, 1776.3 (C=O Ester), 1660 (C=O str), 2981.7 (C-H Ali).
UV (λ_{max})		261 nm
IR (ν_{max})		3334.7 (N-H str), 1720.4 3064.7 (C-H Ar), 2948.9 (C-H Ali), 1753 (C=O Ester), 1591.16 (C=C), 748.33 (C-Cl).

ISSN: 0976-7126
Soni *et al.,* 12(9):11-34, 2021

Figure.No. : Antibacterial activity of 2(substituted phenyl carboxamido)-4-(o-ethyl acetate oxy phenyl) thiazole



ISSN: 0976-7126
Soni *et al.*, 12(9):11-34, 2021



Antimicrobial activity

Antibacterial Activity

Stock solutions of the synthesized compounds and standard drug used were prepared in dimethylsulfoxide taken in the concentration of 100µg/0.1mL.

Standard cultures of Gram positive bacteria viz: *Staphylococcus aureus and Bacillus subtilus and* Gram negative bacteria viz: *Escherichia coli and Klebsiella pneumoniae* species were obtained from Department of Pharmacognosy, Al-Ameen College of Pharmacy, Bangalore. The microorganisms were identified by various staining techniques and bio-chemical reactions. The microorganisms were maintained by sub- culturing and used at regular intervals in nutrient agar medium.

The suspensions of all the organisms were prepared as per Mac-Farland Nephelometer Standard (Baily and Scott 1990). A 24 hr old culture was used for the preparation of bacterial suspension. Suspensions of organisms were made in sterile isotonic solution of sodium chloride (0.9% w/v) and the turbidity was adjusted.

Preparation of assay media:

Sl. No.	**Ingredients**	**Weight (g)**
1.	Beef extract	4.0
2.	Peptone	5.0
3.	Agar	20.0
4.	Distilled water	q.s. 1000 ml
5.	pH	` 5.4

The above-mentioned quantities of different ingredients were accurately weighed and dissolved in appropriate amount of distilled water. Media so prepared was sterilized by autoclaving at 121□C for 15 minutes.

Procedure:

The petridishes were thoroughly washed and sterilized in hot air oven at 160° C for one hr. Inoculum was added to 30 ml of sterile nutrient agar medium and was poured into sterile petridishes for solidifying. Bores were made on the medium using sterile borer. 0.1ml of test solution was added to the respective bores, 0.1ml of the Amoxycillin at a concentration of 100 □g/ 0.1ml was taken as standard reference. A control having only DMSO in the cup was maintained in each plate.

The petridishes were kept in the refrigerator at 4^0 C for 15 minutes for diffusion to take place. After diffusion, the petridishes were incubated at 37^0 C for 24 hr and zones of inhibition were observed and measured using a scale.

Antibacterial activity of all the compounds was carried out against all four microorganisms. The same media was used both for subculturing and for estimating antibacterial activity. The various results are summarized in the Table .

TABLE :- Anti bacterial activity of 2 (substituted phenyl carboxamido)-4- (o-ethyl acetate oxy phenyl) thiazole (GKRS 1-8)

Sl. No.	Compound code	Zone of inhibition in mm			
		S.a	***B.s***	***E.c***	***K.p***
1	GKRS-1	09	12	08	21
2	GKRS-2	12	11	Nil	09
3	GKRS-3	14	20	12	20
4	GKRS-4	Nil	17	06	Nil
5	GKRS-5	10	16	13	20
6	GKRS-6	07	12	14	09
7	GKRS-7	08	12	Nil	07
8	GKRS-8	11	08	15	Nil
Control	DMSO	-	-	-	-
STD	Amoxycillin	25	27	23	28

S.a: Staphylococcus aureus *B.s: Bacillus subtilis* *E.c: Escherichia coli* *nb K.p: Klebsiella pneumoniae*

Antifungal Activity

Stock solutions of the synthesized compounds and standard drug were prepared in DMSO in the concentration of 100 µg / 0.1 ml.

Standard cultures of *Candida albicans* and *Aspergillus niger* were obtained from Department of Pharmacognosy, Al-Ameen College of Pharmacy, Bangalore. The fungi were maintained by subculturing and used at regular intervals.

Nutrient Medium: Sabouraud's agar medium:

Sl.No	Ingredients	Weight in g
1	Dextrose	40
2	Peptone	10
3	Agar	20
4	Distilled water	q.s. 1000 ml

5	pH	5.6

This medium was used for both sub culturing and also for estimating the antifungal activity. The pH of the medium plays an important role for the growth of fungi. Acidic medium favours the growth but excess of acid may not come agar to solidify. Hence the pH of medium was adjusted using 0.1% lactic acid.
The above mentioned quantities of different ingredients were accurately weighed and dissolved water.
The medium so prepared was sterilized by autoclaving at 121^0 C for 15 minutes

An inoculum was prepared by suspending a single isolated colony in about 5 ml of normal saline. This is mixed slowly to achieve a smooth suspension. Later one drop of tween 20 was added for filamentous fungi and the mould was broken by shaking. A sterile cotton swab was moistened in the inoculum suspension and excess of moisture was removed by rolling the cotton swab on the inside of the tube, above fluid level 30 ml of sterile hot Sabouraud's agar medium was poured in each plate and allowed to harden on a level surface. The surface of Sabouraud's agar medium plate was streaked with the help of moistened cotton swab in all the direction ions. The surface of Sabouraud's agar plate was dried out 35^0 C. Later 5 bores per plate were made using sterile cork borer. The above operation was carried out in asceptic condition and 0.1 ml test solution was added to the respective bore and 0.1 ml Amphotericin B was taken as standard reference.
A control having only DMSO was maintained in each plate. The plates are incubated at 35^0 C for 48 hr. Later the values of zones of inhibition were recorded. The various results are summarized in the Table. .

TABLE. :- Anti bacterial activity of 2 (substituted phenyl carboxamido)-4- (o-ethyl acetate oxy phenyl) thiazole (GKRS 1-8)

Sl.No	**Compound code**	**Zone of inhibition in mm**	
		C.a	***A.n***
1	GKRS-4	07	14
2	GKRS-5	09	12
3	GKRS-6	08	16
4	GKRS-7	12	11
5	GKRS-8	15	16
6	GKRS-9	Nil	10
7	GKRS-10	06	08
8	GKRS-11	10	Nil
Control	DMSO	-	-

STD	Amphotericin B	19	18

Conclusion

Many important biochemical compounds and drugs of natural origin contain heterocyclic rings. The presence of a heterocyclic ring in such diverse type of compounds is strongly indicative of profound effects of such molecules to exert physiological activity and recognition of this is reflected abundantly in efforts to find useful synthetic drugs. So synthesis of newer chemical entities has become imperative.

The main focus of this research work has been designed to thiazole moiety to arrive at a newer pharmacophore which has potential antimicrobial activity.

Gives an introduction to the development, biological importance endowed by compounds containing thiazole ring systems.

A brief chemistry and synthetic methods of thiazole also been illustrated.

Focuses on the research work being carried out by explaining the need to develop newer molecules as antimicrobials.

An elaborate review of literature of various substituted thiazole ring systems with their biological activities has been described.

Gives the details regarding the chemicals and reagents used in the entire research work. This section also provides the synthetic schemes used to synthesize the intermediates I, II, III and GKRS- (1,2,3,4, 5,6)

The reaction of o-hydroxy acetophenone and ethyl chloroacetate in NaOH gave Ethyl-o- acetoxyl phenoxyacetate which on bromination in chloroform gave Ethyl (o- bromoacetyl) phenoxyacetate which was further cyclized to gave Ethyl [o-(2-amino-4- thiazolyl)] phenoxyacetate. This was condensed with different aromatic acids to gave substituted derivatives. The physical constants, TLC, recrystallisation solvents of the synthesized compounds were also incorporated in this section.

The structures of the compounds synthesized were assigned on the basis of IR, ^{1}HNMR and elemental analysis.

All the compounds synthesized were evaluated for their invitro antibacterial activity against the Gram +ve and Gram -ve bacteria using the standard drug Amoxycillin.

The synthesized compounds were even evaluated for their antifungal activity against *Candida albicans* and *Aspergillus niger*.

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