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SYNTHESIS OF ADVANCE THIAZOLE DERIVATIVES AND ESTIMATION OF THEIR ANTIMICROBIAL PROSPECTIVE

Somesh M. Bawane*, Pranali R. Gajbhiye, Nitin B. Kohale, Abhijit R. Raut, Ashwini D. Uke, Naresh D. Masankar, Dipali S. Doifode and Nikita P. Aware

Kamalprakash Pharmacy College and Research Centre, Kherda, Karanja (Lad), Dist. Washim, 444105, Maharashtra, India.

***Corresponding Author: Somesh M. Bawane**
Kamalprakash Pharmacy College and Research Centre, Kherda, Karanja (Lad), Dist. Washim, 444105, Maharashtra, India.

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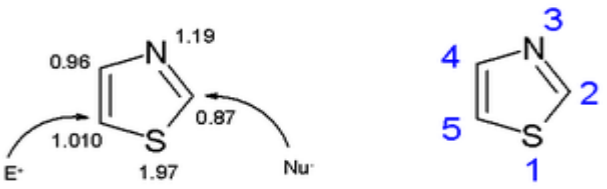
ABSTRACT
Thiazole, or 1,3-thiazole, is a heterocyclic compound that contains both sulfur and nitrogen; the term thiazole also refers to a large family of derivatives. Thiazole itself is a pale-yellow liquid with a pyridine-like odor and the molecular formula C_3H_3NS. The thiazole ring is notable as a component of the vitamin thiamine (B1). In the present study, an attempt has been made to synthesize and characterize some thiazole derivatives and to evaluate them for their antimicrobial activity. Compound Ia, Ib, IIa IIc and IIIb are effective against Gram-positive bacteria and compound Ib, IIa, IIIa, IIIb and IIIc are effective against Gram-negative bacteria. Only compound IIc and IIIc are effective against A. niger as compared with standard. Further, there is a large scope for development of other derivatives and their pharmacological screening. Since, the synthetic scheme is simple and now well established it would be easy to synthesize other derivatives by incorporating various substitutions and screening them for other pharmacological activities like anticancer, anticonvulsant and antiviral.

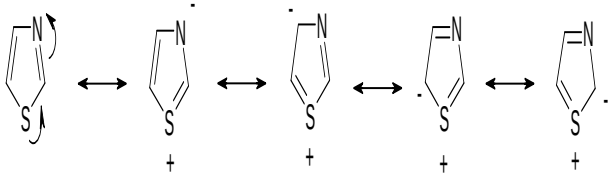
KEYWORDS: Synthesis, Thiazole, Estimation, Gram-positive bacteria, Gram-negative bacteria.

INTRODUCTION
Thiazoles are found in a variety of specialized products, often fused with benzene derivatives, the so-called benzothiazoles. In addition to vitamin B 1, the thiazole ring is found in epothilones. Other important thiazole derivatives are benzothiazoles, for example, the firefly chemical luciferin. Whereas thiazoles are well represented in biomolecules, oxazole are not. Commercial significant thiazoles include mainly dyes and fungicides. Thifluzamide, Tricyclazole, and Thiabendazole are marketed for control of various agricultural pests. Another widely used thiazole derivative is the non-steroidal anti-inflammatory drug Meloxicam.

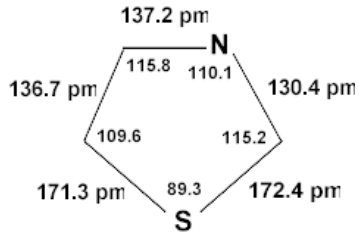
Thiazoles are members of the azoles heterocycles that includes imidazole and oxazole. Thiazole can also be considered a functional group. Thiazole rings are planar and aromatic Thiazoles are characterized by larger pi-electron delocalization than the corresponding oxazole and have therefore greater aromaticity The calculated pi-electron density marks C 5 as the primary site for electrophilic substitution, and C 2 as the site for nucleophilic substitution.



Thiazole is aromatic on the basis of delocalization of a lone pair of electrons from the sulfur atom completing the needed 6 π electrons to satisfy Huckel's rule. The resonance forms are:



Microwave spectra reveal the bond lengths and bond angles in the thiazole molecule. Notice that the C-S bonds are longer than the others because of the larger sulfur atom radius.[1]



Synthesis

Various laboratory methods exist for the organic synthesis of thiazoles.

1. The Hantzsch thiazole synthesis (1889) is a reaction between haloketones and thioamides. For example, 2,4-dimethylthiazole is synthesized from acetamide, phosphorus pentasulfide, and chloroacetone.
2. The Cook–Heilbron thiazole synthesis is the chemical reaction of α-aminonitriles with carbon disulfide to form 5-amino-2-mercapto-thiazoles. Thiazole can also be synthesized by methods as Robinson-Gabriel synthesized, Herz reaction. Thiazoles obtained from microbial and marine origins exhibit antitumor and antiviral activities.[2]

Antimicrobial agents

Chemical compounds biosynthetically or synthetically produced which either destroy or usefully suppress the growth of metabolism of a variety of microscopic or submicroscopic forms of life. On the basis of their primary activity, they are more specifically called antibacterial, antifungal, antiprotozoal, antiparasitic or antiviral agents.

An antimicrobial is a substance that kills or inhibits the growth of microbes such as bacteria (antibacterial activity), fungi (antifungal activity) and viruses (antiviral activity).[3]

MATERIAL AND MEHTOD

All the solvents, chemicals and drugs employed for the synthetic work were of Loba Chemie/ Qualligens/ E. Merck/ Laboratory grade. The percentage yields are based upon the products obtained after purification through crystallization. The solvents used for crystallization has been mentioned within brackets after melting point. The melting points of the compounds were determined in open capillary method. The melting points were mentioned and are in centigrade.

Silica gel G plates (activated at 110 o C, 30 min) were used for thin layer chromatography and the spots were developed in iodine vapor chamber. Different solvent systems were employed for every compound. R f values was reported for better comparable solvent systems.[4]

Identification of chemicals

The melting point of chemical compound was determined by capillary method.[5]

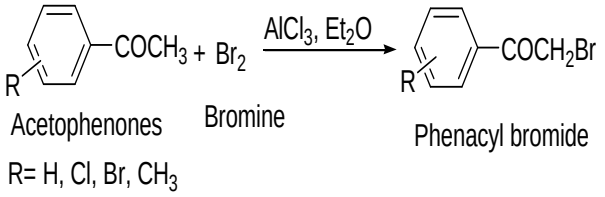
Table no. 1: Identification of chemicals.

Sr. No.	Chemical name	Melting Point
1.	Acetophenone	19-21^{0}C
2.	p-Chloro acetophenone	20-22^{0}C
3.	p-Bromo acetophenone	48-50^{0}C
4.	p-Methyle acetophenone	28-29^{0}C
5.	Aluminium chloride	191-193^{0}C
6.	Aniline	182-183^{0}C
7.	p-Chloro aniline	72-74^{0}C
8.	p-Methyl aniline	65-66^{0}C
9.	Ammonium thiocyanate	147-149^{0}C

Scheme for synthesis of substituted 1,3-Thiazole, 2-amine derivatives

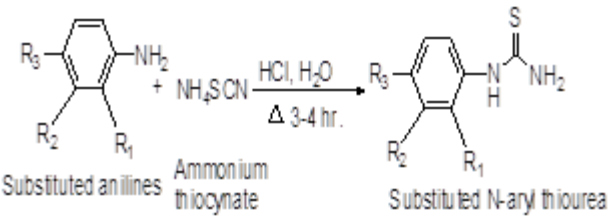
Synthesis of phenacyl bromides (I-III)[6-7]

Various substituted acetophenones were reacted with bromine in presence of a lewis acid, $AlCl_3$ with stirring under ice-cold conditions in anhydrous ether to afford various substituted phenacyl bromides



Synthesis of substituted N-phenyl thioureas (a-c)

Appropriate aniline, ammonium thiocyanate and HCl (30% v/v) in equimolar quantities were reacted together in water for 3-4 hr. to afford various substituted thioureas.

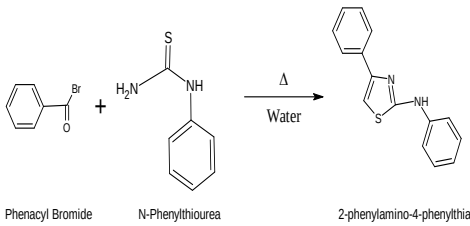


Synthesis of substituted 1,3-Thiazole, 2-amine derivatives (Ia-Ic, IIa-IIc, IIIa-IIIc.)

A series of 1,3-Thiazole, 2-amine derivatives (Ia-c to IIIa-c) were synthesized by condensing with a use of water as solvent.

Method

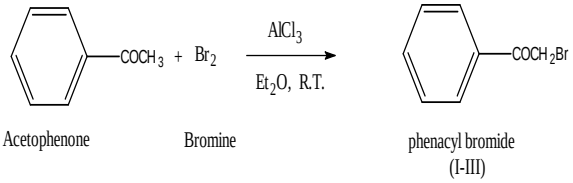
Phenacyl bromide and N-phenyl thiourea in water were heated for appropriate time to afford 2-phenylamino-4-phenylthiazole.



General procedure for synthesis

General procedure for synthesis of compound Ia-Ic, IIa-IIc and IIIa-IIIc.

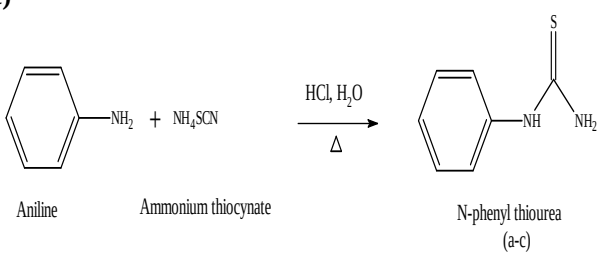
Step 1: Synthesis of substituted phenacyl bromides (1-III)[8]



A solution of (50 g/ 0.42 mole) of acetophenone in 50 ml of pure anhydrous ether were placed in a dry three necked flask fitted with a seperatory funnel, mechanical stirrer and reflux condenser. Reaction mixture was allowed to refluxed, then solution was cooled in an ice-bath, 0.5g of anhydrous $AlCl_3$ was introduced and (67 g, 0.42 mole) of bromine was added gradually from the seperatory funnel with stirring, at the rate of about 1ml per min. The bromine colour was disappeared rapidly with the evolution of HBr, towards the end of the reaction and the solution was becames pink. The phenacyl bromide was remain as a solid mass of brownish-yellow crystals. The colour was removed by shaking with a mixture of 10 ml of water and 10 ml of petroleum ether (60-80°C). The crystals were filtered with suction and washed several times with fresh solvent mixture, until a white product was obtained.

All the substituted phenacyl bromides were prepared by the above method by the bromination of the corresponding substituted acetophenones (0.0035 mole) with Br_2 (0.0035 mole).

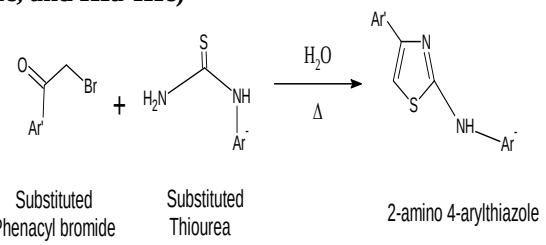
Step 2: Synthesis of substituted N-phenylthioureas (a-c)[9]



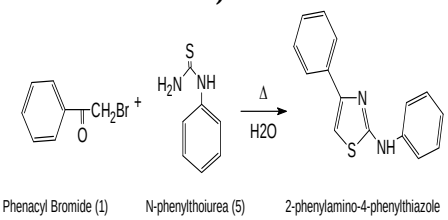
In a RBF aniline (9.3 g, 0.1 mol), ammonium thiocyanate (7.6 g, 0.1 mol) and conc. HCl (11 ml, 30% w/v 0.3 mol) were mixed together with addition of water (100-150 ml). Boiled for 3-4 hr on a heating mantle with periodic replenishment of the water evaporated. The reaction was allowed for overnight at room temperature. Next day separated solid was filtered and washed with 10 ml chilled water. The product was dried without purification.

All substituted N-aryl thioureas were prepared by the above method by the reaction of substituted anilines (0.1 mole) ammonium thiocyanate (0.1 mole) and conc. HCl (30% w/v 0.3 mole), in water.

Step 3: Synthesis of Target Compounds (Ia-Ic, IIa-IIc, and IIIa-IIIc)



Synthesis of N,4-diphenyl-1,3-thiazol-2-amine (General Procedure)



Substituted Phenacyl bromide (1g, 0.005 mole), Substituted N-phenyl thiourea (0.76g, 0.005mole) and water (5ml) were taken in 50ml RBF. The RBF was fitted with condenser and the reaction mixture was heated for appropriate time. After the completion of reaction was indicated by TLC, the solid separated was filtered, washed with water. The crude product on recrystallization from ethanol yielded crystals (1.05g, 87.5%).

Spectral data of synthesized compounds

Infrared absorption spectrum of compound[10]

The potassium bromide pellets containing compound was prepared to record the spectrum in the range of 4000-500 cm^{-1} by using FT-IR spectrophotometer.

H 1 NMR spectrum of compound (Ic)

The H 1 NMR of Ic was taken using Deuterated Chloroform (CDCl 3) as a Solvent

Mass spectrum of compound (IIb)

The mass spectrum of the compound, IIb, reveals a prominent (M^+) peak at 366 amu. Prominent peaks are

seen at m/e 366, m/e 329, m/e 285, m/e 250, m/e 159, m/e 133 and m/e 89, due to the fragments depicted

Antibacterial and Antifungal screening[11]

The preliminary antibacterial activity of synthesized compounds was studied against *E. coli*, *S. aureus* and antifungal activity of compounds were studied against *A. niger* Ciprofloxacin and Miconazole were used as standard for antibacterial and antifungal activity respectively. The agar dilution method was performed using Muller- Hinton agar (Hi-Media) medium for antibacterial activity and Sabouraud's dextrose agar (Hi-Media) medium for antifungal activity. This method depends on the diffusion of drug from bore through the solidified agar layer of a petri dish to an extent such that growth of the inoculated micro-organism is prevented entirely in a circular area "zone" around the cup containing the solution of a compound under test. The medium was sterilized by autoclaving at 12-15 lb pressure for 30 minutes. One loopful of the stock culture was inoculated at 10 ml of agar slant previously in sterilized test tubes, and incubated at 370 C for 24 hrs and 7 days respectively for bacteria and fungi. About 3 ml of distilled water was added to the test tube and a suspension of the culture was obtained by shaking for few minutes.

RESULT AND DISCUSSION

Physicochemical properties[12]

Compounds	Colour	Melting Point* (^{0}C)	Yield (%)	Molecular Formula (Mol. Wt.)	R_f Value**
Ia	White to off white	134-136	87.5	$C_{15}H_{12}N_2S$ (252)	0.53#
Ib	White to off white	148-150	86	$C_{15}H_{11}ClN_2S$ (286)	0.56#
Ic	Greenish white	115-117	87.37	$C_{16}H_{14}N_2S$ (266)	0.57#
IIa	White	103-105	91.01	$C_{15}H_{11}BrN_2S$ (331)	0.57#
IIb	White	140-142	84.17	$C_{15}H_{10}BrClN_2S$ (365)	0.54#
IIc	Greenish	129-131	83.25	$C_{16}H_{13}BrN_2S$(345)	0.58#
IIIa	Brownish White	137-139	86.37	$C_{15}H_{11}ClN_2S$(286)	0.58#
IIIb	Greenish	231-233	90.38	$C_{15}H_{10}Cl_2N_2S$ (321)	0.55#
IIIc	Brownish White	168-170	83.25	$C_{16}H_{13}ClN_2S$ (300)	0.57#

FT-IR Spectrum of synthesied compound[13]

The synthesis procedure is given in scheme. The compound (I-III) display characteristic absorption bands in IR spectrum at 3048.25 cm-1 due to C-H stretching, at 1686.52 cm-1 due to C=O stretching in carbonyl C and C-Br stretching at 563.77. The compound (a-c) display characteristic absorption bands at 3424.01 cm-1 due to aromatic N-H stretching and 1041.19 cm-1 due to C=S stretching in the ring. The compound (Ia) displays characteristic absorption bands at 3371.50 cm-1 due to N-H stretching, 2923.31 cm-1 due to aromatic C-H stretching and 1550.30 cm-1 due to aromatic C=C stretching. The absence of the characteristic carbonyl stretching vibrations indicates that the product (Ia) is cyclized.

Identification and Purification of chemicals[14]

Substituted acetophenones, bromine, aluminium chloride, ammonium thiocyanate, substituted anilines were tested for their identification and purity. The identification and purity of Substituted acetophenones, bromine, aluminium chloride, ammonium thiocyanate, substituted anilines were confirmed by determining melting point. The result of melting point was found to be very closed to reported value. Solvents play an integral role in synthesis as well as in recrystallization. Thus, it is necessary to use solvents of good quality and purity.

Synthesis[15]

The synthesis procedure given in the scheme comprises of three steps:

In the first step the reaction between Substituted acetophenone with Bromine in the presence of Aluminium chloride and Anhydrous ether gave 2-bromo-1-(4-substituted phenyl)-ethanone i.e. substituted phenacyl bromide (I-III).

In the second step the reaction between Substituted aniline with Ammonium thiocyanate in the presence of Hydrochloric acid and water gave 1-(4-substituted phenyl) thiourea (a-c) In last step of reaction 2-bromo-1-(4-substituted phenyl)-ethanone i.e. substituted phenacyl bromide (I-III) with 1-(4-substituted phenyl) thiourea (a-c) gave N-(4-substituted phenyl)-4-(4-substituted phenyl)-1,3-thiazol-2-amine (Ia-Ic, IIa-IIc and IIIa-IIIc) The synthesis procedure is given in scheme. The spectral data of synthesized compound (Ia-Ic, IIa-IIc and IIIa-IIIc). The compound (I-III) display characteristic absorption bands in IR spectrum at 3048.25 cm-1 due to C-H stretching, at 1686.52 cm-1 due to C=O stretching in carbonyl C and C-Br stretching at 563.77. The compound (a-c) displays characteristic absorption bands at 3424.01 cm-1 due to aromatic N-H stretching and 1041.19 cm-1 due to C=S stretching in the ring. The compound (Ia) displays characteristic absorption bands at 3371.50 cm-1 due to N-H stretching, 2923.31 cm-1 due to aromatic C-H stretching and 1550.30 cm-1 due to aromatic C=C stretching. The absence of the characteristic carbonyl stretching vibrations indicates that the product (Ia) is cyclized.

A) N,4-diphenyl-1,3-thiazol-2-amine (Ia)

Yield 87.5%, colour-white to off white, molecular weight 252, melting point 134-136ºC, UV λmax (Log ε MeOH) - 287 Log ε :2.5, IR (KBr) 3371.50 cm-1 (N-H stretching), 2923.31 cm-1 (Aromatic C-H stretching), 1550.30 cm-1 (Aromatic C=C stretching). R f value 0.53 (n-hexane:Ethyl acetate, 4.5:0.5).

B) N-(4-chlorophenyl)-4-phenyl-1,3-thiazol-2-amine (Ib)

Yield 86%, colour-white to off white, molecular weight 286, melting point 148-150 ºC, UV λmax (Log ε MeOH) - 283; Log ε:2.5, IR (KBr) 3370.00 cm-1 (N-H stretching), 2925.00 cm-1 (Aromatic C-H stretching), 1458.37 cm-1 (Aromatic C=C stretching), 729.81 cm-1 (C-Cl stretching). R f value 0.56 (n-hexane:Ethyl acetate, 4.5:0.5).

C) N-(4-methylphenyl)-4-phenyl-1,3-thiazol-2-amine (Ic)

Yield 87.37%, colour-greenish white, molecular weight 266, melting point 115-117 ºC, UV λmax (Log ε MeOH) - 291; Log ε :2.2, IR (KBr) 3243.00 cm-1 (N-H stretching), 2919.72 cm-1 (Aromatic C-H stretching), 1578.02 cm-1 (Aromatic C=C stretching). R f value 0.57 (n-hexane:Ethyl acetate, 4.5:0.5).

D) 4-(4-bromophenyl)-N-phenyl-1,3-thiazol-2-amine (IIa)

Yield 91.01%, colour- white, molecular weight 331, melting point 103-105 ºC, UV λmax (Log ε MeOH) - 285; Log ε :2.4, IR (KBr) 3110.00 cm-1 (N-H stretching), 2991.72 cm-1 (Aromatic C-H stretching), 1578.02 cm-1 (Aromatic C=C stretching), 581.37 cm-1 (C-Br stretching). R f value 0.57 (n-hexane:Ethyl acetate, 4.5:0.5).

E) 4-(4-bromophenyl)-N-(4-chlorophenyl)-1,3-thiazol-2-amine (IIb)

Yield 84.17%, colour-white, molecular weight 365, melting point 140-142ºC, UV λmax (Log ε MeOH) - 289; Log ε:2.4, IR (KBr) 3317.45 cm-1 (N-H stretching), 2885.00 cm-1 (Aromatic C-H stretching), 1587.00 cm-1 (Aromatic C=C stretching), 592.30 cm-1 (C-Br stretching). R f value 0.54 (n-hexane:Ethyl acetate, 4.5:0.5).

F) 4-(4-bromophenyl)-N-(4-methylphenyl)-1,3-thiazol-2-amine (IIc)

Yield 83.25%, colour-greenish, molecular weight 345, melting point 129-131 ºC, UV λmax (Log ε MeOH) - 285; Log ε :2.5, IR (KBr) 3061.16 cm-1 (N-H stretching), 3032.23 cm-1 (Aromatic C-H stretching), 1573.98 cm-1 (Aromatic C=C stretching), 579.94 cm-1 (C-Br stretching). R f value 0.58 (n-hexane:Ethyl acetate,4.5:0.5).

G) 4-(4-chlorophenyl)-N-phenyl-1,3-thiazol-2-amine (IIIa)

Yield 86.37 %, colour-brownish white, molecular weight 286, melting point 137-139ºC, UV λmax (Log ε MeOH) - 303; Log ε:2.3, IR (KBr) 3370.00 cm-1 (N-H stretching), 2925.00 cm-1 (Aromatic C-H stretching), 1458.37 cm-1 (Aromatic C=C stretching), 729.81 cm-1 (C-Cl stretching). R f value 0.58 (n-hexane:Ethyl acetate,4.5:0.5).

H) N,4-bis(4-chlorophenyl)-1,3-thiazol-2-amine (IIIb)

Yield 90.38 %, colour-greenish, molecular weight 321, melting point 231-233 ºC, UV λmax (Log ε MeOH) - 294; Log ε:2.2, IR (KBr) 3335.43 cm-1 (N-H stretching), 2922.18 cm-1 (Aromatic C-H stretching), 1570.74 cm-1 (Aromatic C=C stretching), 719.58 cm-1 (C-Cl stretching). R f value 0.55 (n-hexane:Ethyl acetate, 4.5:0.5).

I) 4-(4-chlorophenyl)-N-(4-methylphenyl)-1,3-thiazol-2-amine (IIIc)

Yield 83.25%, colour- brownish white, molecular weight 300, melting point 168-170ºC, UV λmax (Log ε MeOH) - 292; Log ε:2.4, IR (KBr) 3406.44 cm-1 (N-H stretching), 3091.06 cm-1 (Aromatic C-H stretching), 1504.54 cm-1 (Aromatic C=C stretching), 858.83 cm-1 (C-Cl stretching). R f value 0.57 (n-hexane:Ethyl acetate,4.5:0.5).

Antimicrobial activity[16]

In vitro antimicrobial activities of synthesized compounds were studied by cup plate method using Ciprofloxacin and Miconazole as standard for antibacterial and antifungal activity respectively. The synthesized compounds were evaluated for their anti-bacterial activity against S. aureus and E. coli and antifungal activity against A. niger. The activity of synthesized compounds was reported by measuring the diameter of inhibition zone (in mm). The results showed that synthesized compounds Ia, Ib, IIa IIc and IIIb exhibited good antibacterial activity against S. aureus and compound Ib, IIa, IIIa, IIIb and IIIc shows good antibacterial activity against E. coli at the concentration of 500 µg/ml when compared with the ciprofloxacin. Out of all derivatives, compound Ib is more effective against all tested strains of bacteria at the concentration of 500 µg /ml. The result of antifungal activity showed that compound IIIc is more effective against A. niger at the concentration of 500 µg /ml, where as compound IIc is effective as compared with the standard miconazole. All compounds were found to be ineffective at concentration of 50 µg /ml against all tested strains of fungi.

Table no. 2: Antimicrobial activity data of synthesized compounds (Ia-Ic, IIa-IIc and IIIa-IIIc).

Compound	Bacteria/Fungi Along with zone of inhibition (mm)											
	S. aureus				*E. coli*				*A. niger*			
	50 µg/ml	100 µg/ml	200 µg/ml	500 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml	500 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml	500 µg/ml
Ia	07	10	12	14	_	05	07	08	08	11	12	15
Ib	08	11	13	19	_	_	08	11	10	11	13	15
Ic	_	_	05	07	_	_	07	10	_	_	06	08
IIa	06	08	11	12	_	05	07	11	08	10	12	13
IIb	_	_	_	09	_	05	07	10	07	09	10	13
IIc	08	12	13	15	_	06	09	10	09	11	13	17
IIIa	_	_	05	10	_	09	12	18	08	10	13	15
IIIb	_	_	05	12	09	11	13	15	_	05	08	12
IIIc	_	_	05	07	_	06	07	12	_	10	15	20
Ciprofloxacin	17	18	22	24	14	18	22	25	_	_	_	_
Miconazole	_	_	_	_	_	_	_	_	15	20	24	30

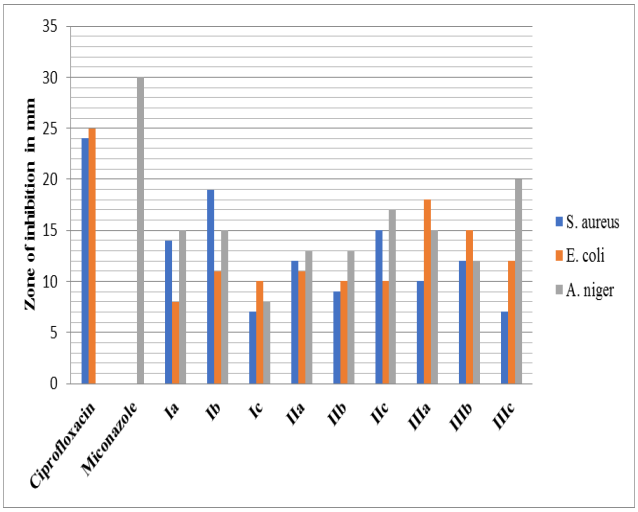


Fig.1: Antimicrobial activity of synthesized compounds (Ia-Ic, IIa-IIc and IIIa-IIIc).

CONCLUSION

In the present study, an attempt has been made to synthesize and characterize some thiazole derivatives and to evaluate them for their antimicrobial activity. The compounds were prepared as per reported procedure in literature with a good yield. The physicochemical characteristic like melting point, % yield, R f value was noted and data is given in Table 4. The infrared spectral analysis of each derivative has been carried out. The in-vitro antimicrobial activity was also carried out by using Ciprofloxacin and Miconazole as standard for antibacterial and antifungal activity respectively. Compound Ia, Ib, IIa IIc and IIIb are effective against Gram-positive bacteria and compound Ib, IIa, IIIa, IIIb and IIIc are effective against Gram-negative bacteria. Only compound IIc and IIIc are effective against A. niger as compared with standard. This states that substitution with 4- methylphenyl, 4-chlorophenyl, bis(4-chlorophenyl) i.e. electron withdrawing groups at position 4 or N of the thiazole ring system favours the more antibacterial activity. Maximum concentration of derivative is required to produce effect, low concentration is not effective. Compound Ib is effective against bacteria and fungi, compound Ic is effective against both tested strains of bacteria but not effective against fungi. As only two compound (IIc-IIIc) shows good antifungal activity and seven compounds (Ia, Ib, IIa IIc, IIIa, IIIb, IIIc) shows antibacterial activity, conclusion can be drawn that thiazole derivatives possess more antibacterial activity than antifungal activity. Further, there is a large scope for development of other derivatives and their pharmacological screening. Since, the synthetic scheme is simple and now well established it would be easy to synthesize other derivatives by incorporating various substitutions and screening them for other pharmacological activities like anticancer, anticonvulsant and antiviral. Thus, by studying all the derivatives showing variety of activities can say that Thiazole ring have been explored in past years and is still be used for future development of new drugs against many more pathological conditions.

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