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Synthesis, Characterization and Biological Evaluation of Novel 2-Alkyl-imidazo[2,1-b]thiazol-3-one

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ABSTRACT

A series of novel Imidazo[2,1-b]thiazole-3-one derivatives substituted at 2-position with several alkyl and aryl group were synthesized, characterized, and their antimicrobial as well as antifungal properties were evaluated. . These compounds were synthesized by formation of sulphide bond in protic solvent using strong base, such as potassium hydroxide or sodium hydroxide, followed by cyclization in presence of mild acid such as silica get or acidic resin. The compounds synthesized were characterized using FTIR, 1H NMR and mass spectroscopy. The compounds synthesized were screened for in vitro activity against *S. aureus, E. coli, P. aeruginosa, S. typhimurium, F. oxysporum* and *A. alternata*. Some of these compounds exhibited moderate to good activity, whereas some were found inactive, against pathogens being evaluated.

Keywords : Imadazone, Thiazole, Imidazo-Thiozole, Antibecterial, Antifungal.

I. INTRODUCTION

Thiazole an important group of heterocyclic compounds has attracted attention of researchers in the field of drug design, specifically after the identification of thiazole moiety in some active compounds and alkaloids like vitamin B1, Penicillin etc. Approximately forty alkaloids are known to have thiazole ring structure, for examples antifiotic coumermycine and acidomycine, anthelmintic micothiazole, macrocyclic alkaloids tantazole, sisomycine to name some of them. In addition to this fused thiazoleamine has attracted considerable attention because of their usefulness, primarily due to a very wide spectrum of biological activities. Thiazole core unit were found to show interesting biological activities such as anti-anoxic[01], allosteric enhancer of adenosine A1 receptors[02], mycobacterium tuberculosis methionine amino peptidases[03], anti-helicobacter pylori (H-pylori) agent[04] and adenosine A2B receptor antagonist[05] . The importance of thiazole moiety is also evident from the fact that it is found in several potent biologically active drugs like Sulfathiazol (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) and Bleomycine and Tiazofurin (antineoplastic drug) . Recently thazole derivatives were found in drug development for treatment of allergies[06], hypertension[07], inflammation[08], schizophrenia[09], bacterial[10], HIV infections[11], hypnotics[12] and more recently for the treatment of pain[13], as fibrinogen receptor antagonists with antithrombotic activity[14]and as new inhibitors of bacterial DNA gyrase B[15].

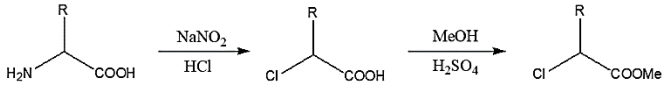
Imidazole is another important scaffolds being extensively investigated for last almost two centuries by researcher for their medicinal application. Our earlier study also demonstrates imidazole derivatives as biologically potential candidates for antibacterial and antifungal activity[16] . This study is aimed to evaluate biological activity of [5-5] member fused bycyclic heterocycles Imidazole and thiazole, i.e. Imidazo-thiazole.

In our endeavor to develop new routes to diversely substituted imidazo-thiazole derivatives, we have explored relatively unexplored imidazo-thiazole scaffold. Several novel derivatives of imidazo-thiazole were prepared and evaluated for their biological activity.

General reaction scheme :

General scheme to synthesis various derivatives of Imidazo-thiazole is given as below.

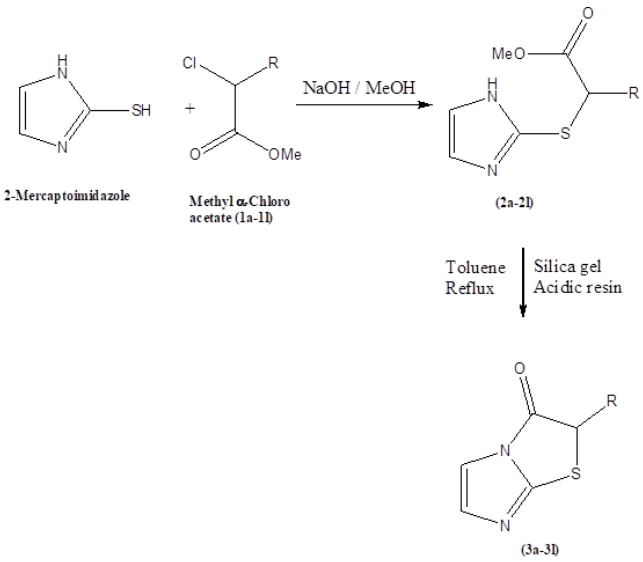
Scheme 1:



Amino acid (AA) — **Methyl α-Chloro acetate (1a-1l)**

a = R : - H, b = R : - CH_3, c = R : - CH_2CH_3,
d= R : - $CH_2CH_2CH_3$, e = R : - $CH_2CH_2CH_2CH_3$, f = R : - $CH(CH_3)_2$,
g = R : - $CH_2CH(CH_3)_2$, h = R : - $CH(CH_3)CH_2$-CH_3, i = R : - $C(=CH_2)CH_3$,
j = R : - CH_2-Ph k = R : -$(CH3)_2$ l = R: -Ph

Scheme 2 :



2-Aklyl-imidazo[2,1-*b*]thiazol-3-one

Various natural as well as un-natural amino acid used in the synthesis to get various derivatives of final Imidazo-thiazole compounds, the details of amino acid used, their structure and respective structural residue resulted in final compound is listed in table 01 and 02.

Table 01 : List of natural amino acid used :

Sr. no	Code	Name of Amino acid used	Amino acid structure	Structure of substituent "-R"	Formula of Substituent "-R"
1	a	Glycine	H_2N COOH	- H	- H
2	b	Alanine	CH_3 H_2N COOH	- CH_3	- CH_3

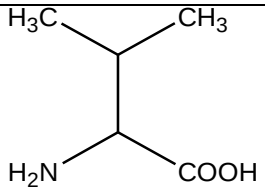
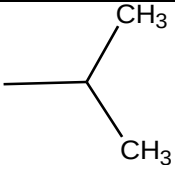
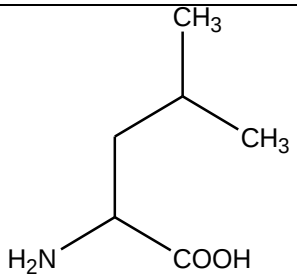
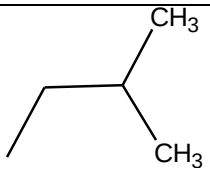
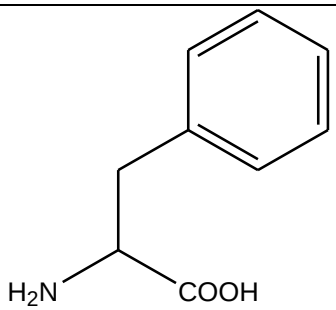
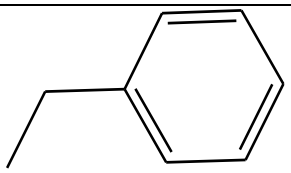
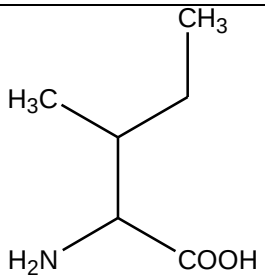
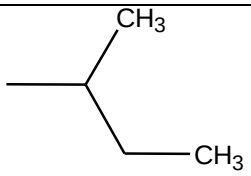
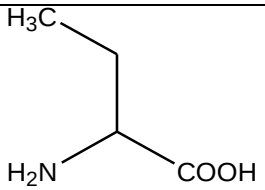
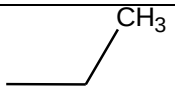
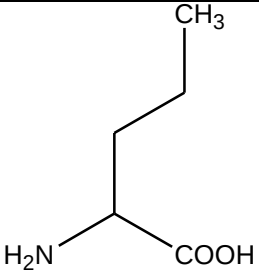
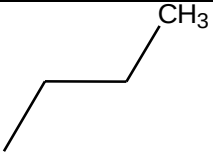
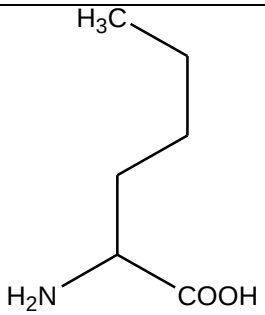
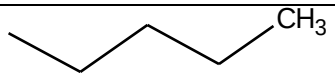
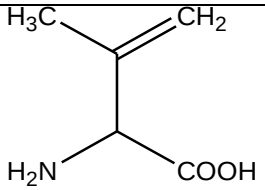
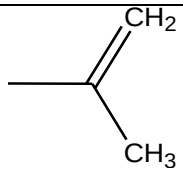
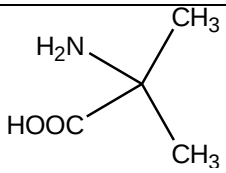
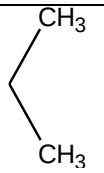
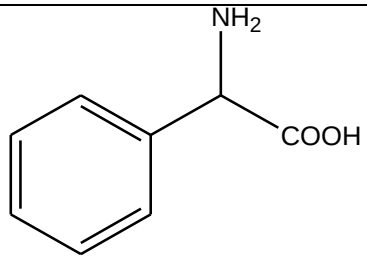
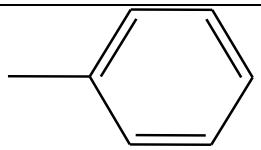
3	f	Valine			- $CH(CH_3)_2$
4	g	Leucine			- $CH_2CH(CH_3)_2$
5	j	Phenyl alanine			- CH_2-Ph
6	h	Isoleucine			- $CH(CH_3)CH_2$-CH_3

Table 02 : List of un-natural amino acid used

Sr. no	Code	Name of amino acid used	Amino acid structure	Structure of substituent "-R"	Formula of Substituent "-R"
1	c	2-Aminobutyric acid			- CH_2CH_3
2	d	Norvaline			- $CH_2CH_2CH_3$

3	e	Norleucine			- $CH_2CH_2CH_2CH_3$
4	i	2-Amino-3-methyl-but-3-enoic acid			- $C(=CH_2)CH_3$
5	k	Dimethyl glycine			-$(CH3)_2$
6	l	Phenyl glycine			-Ph

II. MATERIAL AND METHODS

All chemicals were purchased from laboratory chemical suppliers and used without further purification. Melting points (m.p.) were determined using a Veego VMP-PM melting point apparatus and are uncorrected. Mass spectra (MS) were recorded on a Waters Q-TOF instrument in only positive ion detection mode. The 1H NMR spectra were recorded on a Bruker Avance II 500 (500 MHz) instrument using $CDCl_3$ as solvent and Tetramethyl silane (TMS) as internal reference. Chemical shifts are expressed as δ values (ppm) . IR spectra were recorded on Perkin Elmer spectrum 100 FT-IR spectrophotometer. The course of reactions was monitored and the purity of synthesized compounds was checked by TLC using silica gel 60 F 254 Al-plates (Merck, Germany) in Dichloromethane : Methanol : Acetic acid (80:15:5) and Dichloromethane : Methanol (90:10) as mobile phase and the spots were visualized under 254nm UV illumination and 1 % $KMnO_4$ solution.

Quality of all the **imidazo[2,1-b]thiazol-3-one derivatives** synthesized were achieved by purification till TLC of the compounds show acceptable purity. Most of the compounds showed single spot in TLC, while some of them were having very faint other spots. Visually main spot under 254 nm UV light were estimated to be at least not less than 95%.

Yield data given are overall yield, Mass spectra was done by direct mass analysis, melting points are not corrected and IR peaks were recorded in nm using KBr pallet.

General process for synthesis of 2-Substituted-[(1H-imidazol-2-ylsulfanyl)]-acetic acid methyl ester (2a-2l) : 2-Mercaptoimidazole (0.1 mole, 10g) was dissolved in solution of Sodium hydroxide(0.11mole, 0.44g) in Methanol (50 ml). To this mixture added

solution of suitably substituted methyl α-chloroacetate (0.11 mole) **(1a-1l)** in 2-3 volume Methanol maintaining ambient temperature, mild cooling is required to maintain ambient temperature. The mixture was stirred at ambient temperature for 2 to 3 hours. Reaction mass was monitored using TLC for disappearance of starting material, i.e. 2-Mercaptoimidazole. The heterogeneous reaction mass was filtered and washed with ice-cold Methanol to yield product of sufficient purity to use in next stage. i.e. cyclization.

General procedure for synthesis of 2-Substituted Imidazo[2,1-b]thiazol-3-one (3a-3l) : 2-Substituted-[(1H-imidazol-2-ylsulfanyl)]-acetic acid methyl ester (2a-2l) (0.05mole) and silica gel (60-120 mesh) or acidic resin (1 to 2 g) were suspended in Toluene (150ml) . The heterogeneous mixture was refluxed for 7 to 9 days. Reaction monitoring was done using TLC for disappearance of starting material. After completion of reaction, the reaction mass was distilled off at reduced pressure to get syrup. The syrup was purified using flash column chromatography on silica 230 to 400 mesh using mixture of Dichloromethane and Methanol as mobile phase. Collected fractions were observed pure on TLC and concentrated under reduced pressure to get syrup. Repeated tituration of syrup using Hexane gave product as solid.

Synthesis of Substituted α-Chloro acetic acid methyl ester (1a-1l) :

(i) Synthesis of Substituted α-chloro acetic acid [17]: Dissolved suitable amino acid (0.1 mole) in 5 N Hydrochloric acid (10 volume). Cooled the mixture to 0-5°C and added to that sodium nitrite(0.16 mole, 11g) in Water (4 volume) maintaining temperature below 5°C under vigorous stirring. Reaction was allowed to come to room temperature and then stirred overnight. Reaction is applied mild vacuum under stirring till colour changes from yellowish brown to pare yellow. Slowly added to that Sodium carbonate (10g) . Extracted the reaction mass using Ethyl acetate and organic layer was washed with brine and evaporated on rota-vapour to get product as oil. This product is directly used for preparation of methyl ester.

(ii) Synthesis of Substituted α -Chloro acetic acid methyl ester (1a-1l): The Substituted α-chloro acetic acid obtained above was taken into Round bottom flask, added Methanol (10 vol) and cooled the mass to 10-15°C. Added to that concentrated H_2SO_4 (1.2 mole equivalent with respect to α-chloro acetic acid) . The reaction mass was stirred at ambient temperature and then at 50-60°C overnight. Reaction was monitored using TLC. On completion of reaction, reaction mass was distilled off to get syrup. The syrup was dissolved in Ethyl acetate and washed with brine solution, dried over anhy. Sodium sulphate and concentrated under reduced pressure to get product as syrup. This syrup was directly used in further synthesis.

Imidazo[2,1-b]thiazol-3-one (3a) : Off white solid; Yield : 17 % (Overall); M. P. : 127-131°C; Mol formula : $C_5H_4N_2OS$; M. wt. : 140.1; MS (*m/z*): 141.0 (M + 1); IR (KBr,cm^{-1}): 1757 (C=O) ;1H NMR spectrum in $CDCl_3$ (δ ppm) ; 4.43 (s, 2H, -CH_2-CO-), 7.63 (d, 1H, Ar-H), 7.47 (d, 1H, Ar-H).

2-Methyl-imidazo[2,1-b]thiazol-3-one (3b): White solid; Yield : 21 % (Overall); M. P. : 139 -141°C; Mol formula : $C_6H_6N_2OS$; M. wt. : 154.19; MS (*m/z*): 155.0 (M + 1); IR (KBr,cm^{-1}): 1738 (C=O) ; 1H NMR spectrum in $CDCl_3$ (δ ppm) ; 4.61 (q, 1H, -CH-CO-), 7.62 (d, 1H, Ar-H), 7.48 (d, 1H, Ar-H), 1.81 (d, 3H, -CH_3).

2-Ethyl-imidazo[2,1-b]thiazol-3-one (3c) : Off white powder**;** Yield : 16 % (Overall); M. P. : 143-145°C; Mol formula : $C_7H_8N_2OS$; M. wt. : 168.2; MS (*m/z*): 191.0 (M + Na); IR (KBr,cm^{-1}): 1741 (C=O); 1H NMR spectrum in $CDCl_3$ (δ ppm) : 4.54 -4.64 (m, 1H, -CH-CO-), 7.62 (d, 1H, Ar-H), 7.47 (d, 1H, Ar-H), 2.05 – 2.21 (m, 2H, -CH_2-), 1.20 (m, 3H, -CH_3).

2-Propyl-imidazo[2,1-b]thiazol-3-one (3d); White solid**;** Yield : 13 % (Overall); M. P. : 133-136°C; Mol

formula : $C_8H_{10}N_2OS$; M. wt. : 182.2; MS (*m/z*): 183.0(M + 1); IR (KBr,cm^{-1}): 1733 (C=O); 1H NMR spectrum in $CDCl_3$ (δ ppm) ; 4.63 -4.51 (m, 1H, -CH-CO-), 7.63 (d, 1H, Ar-H), 7.47 (d, 1H, Ar-H), 1.48-1.33 (m, 2H, -CH-C**H**$_2$-CH_2-), 1.29-1.19 (m, 2 H, -CH_2-C**H**$_2$-CH_3), 1.03-0.91 (t, 3H, -CH_2-C**H**$_3$).

2-Butyl-imidazo[2,1-b]thiazol-3-one (3e) : Light brown solid; Yield : 11 % (Overall); M. P. : 125-128°C; Mol formula : $C_9H_{12}N_2OS$; M. wt. : 196.27; MS (*m/z*): 197.1 (M + 1); IR (KBr,cm^{-1}): 1735 (C=O); 1H NMR spectrum in $CDCl_3$ (δ ppm) : 4.61 -4.48 (m, 1H, -CH-CO-), 7.63 (d, 1H, Ar-H), 7.47 (d, 1H, Ar-H), 2.01 -1.89 (m, 2H, -CH-C**H**$_2$-CH_2), 1.41-1.16 (m, 4H, -CH_2- & -CH_2-), 0.98-0.81 (t, 3H, -CH_3).

2-Isopropyl-imidazo[2,1-b]thiazol-3-one (3f); Yield : 9 % (Overall); M. P. : 137-138°C; Mol formula : $C_8H_{10}N_2OS$; M. wt. : 182.24; MS (*m/z*): 183.1 (M + 1); IR (KBr,cm^{-1}): 1729 (C=O); 1H NMR spectrum in $CDCl_3$ (δ ppm) : 4.62 -4.43 (d, 1H, -CH-CO-), 7.62 (d, 1H, Ar-H), 7.48 (d, 1H, Ar-H), 2.49-2.30 (m, 1H, -C**H**-$(CH_3)_2$, 1.41 (d, 6H, -CH-(C**H**$_3$)$_2$.

2-Isobutyl-imidazo[2,1-b]thiazol-3-one (3g): White powder; Yield : 15 % (Overall); M. P. : 148°C; Mol formula : $C_9H_{12}N_2OS$; M. wt. : 196.27; MS (*m/z*): 197.1 (M + 1); IR (KBr,cm^{-1}): 1734 (C=O); 1H NMR spectrum in $CDCl_3$ (δ ppm) : 4.62 -4.50 (m, 1H, -CH-CO-), 7.63 (d, 1H, Ar-H), 7.47 (d, 1H, Ar-H), 1.37-1.22 (m, 2H, -CH-C**H**$_2$-CH-), 1.51-1.39 (m, 1H, -CH_2-C**H**-), 1.01-0.89 (d, 6H, -CH-(C**H**$_3$)$_2$).

2-*sec*-Butyl-imidazo[2,1-b]thiazol-3-one (3h): Off white powder: Yield : 6 % (Overall); M. P. : 137°C; Mol formula : $C_9H_{12}N_2OS$; M. wt. : 196.27; MS (*m/z*): 197.1 (M + 1); IR (KBr,cm^{-1}): 1731 (C=O); 1H NMR spectrum in $CDCl_3$ (δ ppm) : 4.62 -4.46 (d, 1H, -CH-CO-), 7.67 (d, 1H, Ar-H), 7.49 (d, 1H, Ar-H), 2.04-1.89 (m, 1H, -C**H**-CH_2-),1.49-1.32 (m, 2H, CH_2), 1.11-0.89 (m, 6H, -CH_3 & -CH_3).

2-Isopropenyl-imidazo[2,1-b]thiazol-3-one (3i): White slightly sticky solid**:** Yield : 4 % (Overall); M. P. : 160°C; Mol formula : $C_8H_8N_2OS$; M. wt. : 180.23; MS (*m/z*): 181.0 (M + 1); IR (KBr,cm^{-1}): 1719 (C=O); 1H NMR spectrum in $CDCl_3$ (δ ppm) : 5.62 (s, 1H, -CH-CO-), 7.65 (d, 1H, Ar-H), 7.48 (d, 1H, Ar-H), 4.81-4.59 (m, 2H, -C=CH_2**),** 2.22-1.98 (m, 3H, -CH_3**)**.

2-Benzyl-imidazo[2,1-b]thiazol-3-one (3j): Light pink solid; Yield : 29 % (Overall); M. P. : 153-156°C; Mol formula : $C_{12}H_{10}N_2OS$; M. wt. : 230.29; MS (*m/z*): 231.1 (M + 1); IR (KBr,cm^{-1}): 1720 (C=O); 1H NMR spectrum in $CDCl_3$ (δ ppm) : 4.76-4.59 (m, 1H, -CH-CO-), 7.69 (d, 1H, Ar-H), 7.59-7.18 (m, 6H, C_6H_5, -Ar-H), 3.04- 2.38 (m, 2H, -CH-C**H**$_2$-).

2,2-Dimethyl-imidazo[2,1-b]thiazol-3-one(3k): Off white solid; Yield : 7 % (Overall); M. P. : 173-177°C; Mol formula : $C_{12}H_{10}N_2OS$; M. wt. : 168.22; MS (*m/z*): 169.0 (M + 1); IR (KBr,cm^{-1}) : 1727 (C=O); 1H NMR spectrum in $CDCl_3$ (δ ppm) ; 7.67 (d, 1H, Ar-H), 7.48 (d, 1H, Ar-H), 1.7 (s, 6H, 2-CH_3).

2-Phenyl-imidazo[2,1-b]thiazol-3-one(3l) : light yellow solid; Yield : 3 % (Overall); M. P. : 111-112°C; Mol formula : $C_{11}H_8N_2OS$; M. wt. : 216.26; MS (*m/z*): 239.0 (M + Na); IR (KBr,cm^{-1}): 1746 (C=O); 1H NMR spectrum in $CDCl_3$ (δ ppm) ; 5.85 (s, 1H, -CH-CO-), 7.87 (d, 1H, Ar-H), 7.45 (d, 1H, Ar-H), 7.79 – 7.57 (m, 5H, Ar).

Biological screening : Preliminary examination of the biological activity of these newly synthesized compounds was performed by the disc diffusion method[18] using Muller Hinton Agar (MHA) medium. In hard glass screw cap test tube, sterile slants of MHA were prepared. Stored pure cultures were transferred to the freshly prepared MHA slants separately for each organism using sterilized inoculating loop. In this way, four test tubes were freshly prepared for each bacterial pathogen. Freshly prepared pure culture

tubes slants were used for inoculation of nutrient broths. These tubes were incubated at (35+/-2°C) for 24 hours to get bacterial suspensions used to study antibacterial activity. The microorganisms were spread on the surface of MHA plate. Five wells of equal size were created using gel puncher (4 mm) in each plate. These wells were then filled with 10 µL of each sample and labeled accordingly. DMSO was used as a solvent. The micro-organisms of *Staphylococcus aureus* NCIM 2127 (*S. aureus*), *Escherichia coli* NCIM 2065 (*E. coli*), *Pseudomonas aeruginosa* NCIM-2036 (*P. aeruginosa)* and *Salmonella typhimurium* NCIM 2501 (*S. typhimurium*) were purchased from the National Chemical Laboratory (NCL), Pune, India.

TABLE 03 In *vitro* antimicrobial activities for imidazo-thiazole derivatives.

Compound code	Zone of inhibition (in mm)					
	Bacteria				Fungi	
	Gram +ve	Gram -ve				
	S. aureus	*E. coli*	*P. aeruginosa*	*S. typhimurium*	*F. oxysporum*	*A. alternata*
3a	8	4	0	3	4	16
3b	3	4	6	11	11	8
3c	**16**	**9**	**9**	**4**	**33**	**27**
3d	**13**	**8**	7	**5**	**39**	**25**
3e	**19**	**11**	**8**	**7**	**38**	**30**
3f	3	6	2	1	18	13
3g	11	5	4	4	8	9
3h	1	13	7	10	13	32
3i	**17**	**13**	**11**	**9**	**35**	**29**
3j	6	2	6	6	22	13
3k	2	7	3	7	7	5
3l	**14**	**14**	**6**	**11**	**34**	**28**
Ampicillin	18	10	-	-	-	-
Chloramphenicol	12	14	8	10	-	-
Nystatin	-	-	-	-	40	31

III. RESULT AND DISCUSSION

All the compounds synthesized were characterized using various spectroscopic techniques. IR spectra showed characteristic bands of carbonyl bend at 1719 - 1757 confirming existence of carbonyl functionality. The 1H spectrum was recorded at 500 MHz and showed all characteristics pattern of peaks in their respective range. Electron ionization mass spectrometric fragmentation pattern further confirmed the existence of desired compound, giving either M+1 or M+Na peak.

Biological assay : All the synthesized compounds were evaluated *in vitro* for their antibacterial activities against *S. aureus as* examples of Gram positive bacteria and *E. coli, P. aeruginosa and S. typhimurium as* examples of Gram negative bacteria. They were also evaluated *in vitro* for their antifungal activities against the *F. oxysporum* and *A. alternata* fungal strains. The results were compared with the standard 0.3% Ampicillin and Chloramphenicol as antibacterial agent while Nystatin was used as reference drugs as antifungal agent. Results were summarized in Table 03.

Biological activity of Imidazo-thiazole 3-one derivatives bearing substituted ethyl 3c (-CH_2CH_3), propyl 3d (-$CH_2CH_2CH_3$), n-butyl 3e (-$CH_2CH_2CH_2CH_3$), propylene 3i (-$C(=CH_2)CH_3$) and phenyl 3l (-Ph) at 2 position exhibits substantially higher biological activity against the bacterial and fungal pathogen being evaluated when compared to the reference standards Ampicillin, Chloramphenicol and nystatin applied. While compounds with no substituent 3a (R = -H), methyl substituent 3b (R = -CH_3), isopropyl substituent 3f (R = -$CH(CH_3)_2$), sec-Butyl 3g(-$CH_2CH(CH3)2$), isobutyl 3h (-$CH(CH_3)CH_2CH_3$), 2-propene substituent 3i (R = $C(=CH_2)CH_3$) , benzyl substituent 3j (-CH_2-Ph) and dimethyl substituent 3k (-$(CH_3)_2$) observed to have lower biological activity against all the bacterial and fungal pathogens being studied in comparison to reference standard Ampicillin, Chloramphenicol and Nystatin. Overall Imidazo-thiazole substituent with thiazol ring having natural amino acid side chain residue shows comparatively lower biological activity against these pathogens while the unnatural amino acid residue at same position shows significantly higher activity with exception of dimethyl residue which even after bearing un-natural amino acid residue shows very poor biological activity in comparison to other un-natural amino acid residue evaluated in this study.

IV. CONCLUSION

We have disclosed the simple and short process for synthesis of potent and novel "Imidazo-thiazole 3-one" series (3a – 3l), formation of desired compounds was characterized using IR, NMR and Mass spectroscopy. Biological evaluation of these compounds suggests that thiazole ring having natural amino acid side chain residue shows lower biological activity against these pathogens while the unnatural amino acid residue at same position shows significantly higher activity with exception of dimethyl residue which shows very poor biological activity.

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