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Antimicrobial Potential of Nicotinic Acid Derivatives Against Various Pathogenic Microbes

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Abstract

Many human illnesses are caused by infections with microbes like viruses or bacteria or fungi. Amongst those various illnesses, certain tubercular, bacterial, viral and fungal infections are more common because of their tendency to develop new strains under any circumstances and developing resistance against the available drugs. This stimulated the scientists for development of novel molecules to combat these illnesses. Several nicotinic derivatives were evaluated for their antibacterial activity against tuberculosis. This review summarized the facts concerning nicotinic acid analogues. The nicotinic acid moiety of nicotinic acid has been introduced in a number of compounds with antimicrobial activity against various pathogens as well as resistant strains. Several nicotinic acid analogues have shown good antimicrobial activity. Therefore this class of compounds could be a good starting point to develop new lead compounds in the treatment of multi-drug resistant bacteria.

Keywords: Anti-bacterial; anti-fungal; nicotinic acid derivatives; multidrug-resistance.

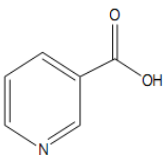
Introduction

Infectious microbial diseases remain a pressing problem worldwide, because microbes have resisted prophylaxis or therapy longer than any other form of life. In world up to 5% of all the infections are caused by fungi. Fungal infections in such a high risk patients progress rapidly and are difficult to diagnose and treat. Infectious diseases caused by bacteria have increased dramatically in recent years. Inspite of many significant advances in antibacterial therapy, the widespread use and misuse of antibiotics have caused the emergence of bacterial resistance to antibiotics, which is a serious threat to public health. In particular, the emergence of multidrug resistant (MDR) gram-positive bacteria, including methicillin-resistant Staphylococcus aureus, vancomycin-resistant S. aureus, and vancomycin-resistant Enterococci has become a serious problem in the treatment of bacterial diseases [1]. Therefore, the development of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. Tuberculosis (TB) is an important health problem worldwide particularly in people infected with HIV virus. Other causes that increasing TB cases are MDR, resulting from inconsistent or partial treatment, and the lack of new drugs in the market [2]. Because of these problems, TB is a global health emergency. This contagious disease is caused by the *Mycobacterium tuberculosis*. One third of the world´s population is infected by the TB bacterium and each year this disease affects around 8 million people and kills almost 3 million people [3]. At present, the treatment

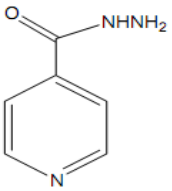
against TB involves 3 or 4 different kinds of anti-TB drugs. These drugs usually are isoniazid, rifampicin, pyrazinamide and ethambutol. Multiple combinations are necessary to prevent the emergence of MDR organisms, which would lead to treatment failure [4, 5]. In spite of TB being a global health problem, about 40 years have past since a new drug was introduced into the market. Consequently, the development of new drugs with fewer toxic side effects, improved pharmacokinetics properties, potent activity against Gram-positive and Gram-negative bacteria, including resistant strains, is urgently needed [6-9].

Nicotinic aids have proven to play a significant role in the synthesis of novel drug candidates with the use of different functional groups. Recently a series of Nicotinic aid derivatives have demonstrated significant antimicrobial activity. These compounds were screened for their wide range of biological activities, anti-TB activity against *M. tuberculosis*, antimicrobial activities against various bacteria, fungi, and yeast species. In addition, nicotinamide and nicotinic acid have been in use for 65 years due to their unusual antimicrobial spectrum. Many drugs possess modified pharmacological and toxicological properties when administered in form of metallic complexes [10-12]. In view of this it was interesting to synthesize several new compounds to evaluate the effect of amino acids on the bioactivity of both benzoic acid hydrazide and nicotinic acid hydrazide. The effect of metals such as Cu and Cd on the antibacterial activity of these compounds, thus both hydrazide ligands and complexes were tested for their antibacterial and antifungal activity.

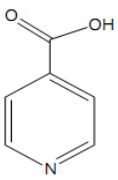
The pyridine nucleus is an important heteroaromatic class of compounds with a wide range of activities and it is present in many products such as drugs, vitamins, food, flavorings, plants, dyes, rubber products, adhesives, insecticides and herbicides [13]. In this context, nicotinic acid (pyridine-3-carboxylic acid), also known as niacin and vitamin B3, is found in various plants and animals and has vital roles in such biological processes as production of energy, signal transduction, regulation of gene expression and synthesis of fatty acids, cholesterol and steroids. Nicotinic acid derivatives and its isomers have also been investigated as an agent for the prevention or delay of the onset of type 1 diabetes mellitus. They also have anti-bacterial, anti-oxidant, anti-inflammatory and anti-carcinogenic activities, and have putative activity against osteoarthritis and granuloma annulare. For example, it can be mentioned the importance of anti-tuberculosis first-line drug Isoniazid [14], which is an analogue of isonicotinic acid, an isomer of nicotinic acid. Nicotinic acid derivatives are also an important start material for the preparation of other biological activity compounds. Considering that, 2-chloro-3-pyridine carbonyl chloride is a useful intermediate for preparation of Nevirapine (Viramune), a valuable anti-AIDS drug [15]. Due to the importance of nicotinic acid derivatives and its isomers, the aim of this article is to evaluate the *in vitro* antibacterial activity against *M. tuberculosis* of several compounds of this class synthesized by our group [16].



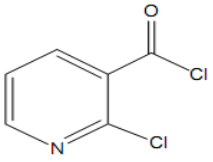
Nicotinic acid



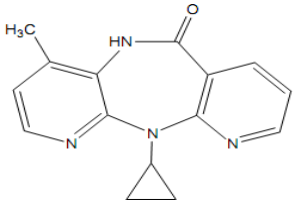
Isoniazid



Isonicotinic acid



2-chloro-3-pyridine carbonyl chloride

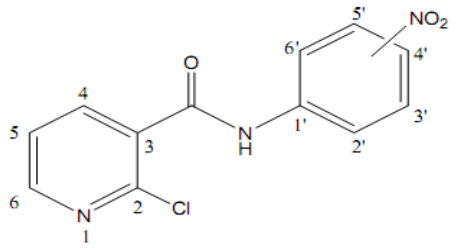


Nevirapine (Viramune)

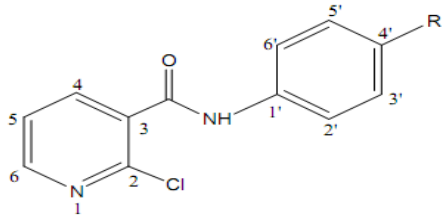
A drug may be classified by the chemical type of the active ingredient or by the way it is used to treat a particular condition. Each drug can be classified into one or more drug classes. Nicotinic acid derivatives are highly specific antibacterial agents. Nicotinic acid derivatives are used for the treatment of microbial infections, as results in the rapid development of resistance. The substituted nicotinic acid is among the various heterocycles that have received most attention during last three decades as potential biomolecules. Nicotinic acid derivatives exhibit antibacterial, antioxidant, anti-inflammatory and anticarcinogenic activities. This pyridine congeners are associated with different biological properties like pesticidal, insecticidal and antifungal activities. Large quantity of nicotinic acid derivatives was equipped for their anti-microbial activities. In prolongation we planned to synthesis some new nicotinic acid derivatives with different substituted groups or atoms and different heterocycle moiety. With the emergence and raise of microbial organisms dead set against to manifold anti-biotic, and the long-lasting emphasis on healthcare costs, many researchers have tried to expand new, valuable anti-microbial reagents free of resistant and cost [17].

Nitro nicotinic derivatives:

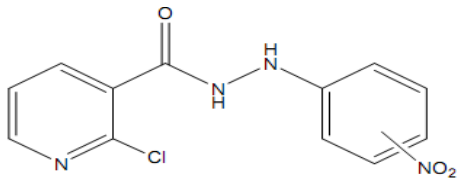
The reaction between 2-chloro-3-pyridinecarbonylchloride and nitro anilines or nitro phenylhydrazines, leading to the compounds **1a-c**, **2a-g**, **3a-c**, and **4a-d** [18-20]. The *N*-nitro-2-chloronicotinamides, as well others *N*-aryl-2-chloronicotinamides were evaluated for their *in vitro* antibacterial activity against *M. tuberculosis* using the Alamar Blue (MABA) susceptibility test and the activity expressed as the MIC in mg/mL. However, none of the compounds above mentioned were active. The 1-(2-chloronicotinoyl)-2-(nitrophenyl) hydrazines **3a-c** were evaluated for their *in vitro* antibacterial activity against *M. tuberculosis* H37Rv using the Alamar Blue susceptibility test and the activity expressed as the MIC in µg/mL. However, none of the compounds above mentioned were active. The compounds **4a-d** were evaluated for their *in vitro* antibacterial activity against *M. tuberculosis* H37Rv using the MABA test and the activity expressed as the MIC in µg/mL. However, none of the compounds above mentioned were active. The anti-TB activities of compounds **1a-c**; **2a-g**; **3a-c**; **4a-d** were assessed against *Mtb* using the micro plate Alamar Blue assay (MABA). A serial dilution of the compounds **1a-c**; **2a-g**; **3a-c** and **4a-d** were made directly on the plate. The final drug concentrations tested were 0.01 to 20.0µL/mL.



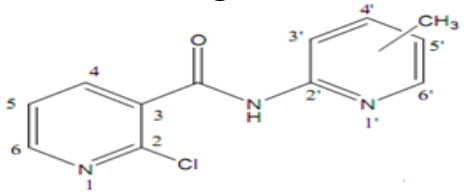
1a: o-nitro; **1b:** m-nitro; **1c:** p-nitro



2a: R=H; **2b:** R=OMe; **2c:** R= Br; **2d:** R=I; **2e:** R= Cl; **2f:** R=F; **2g:** R=CN



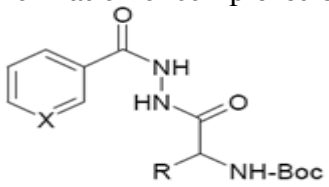
3a: o-nitro; **3b:** m-nitro; **3c:** p-nitro



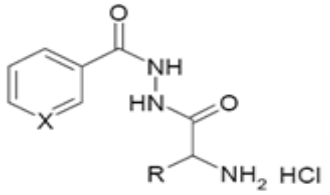
4a:3’-methyl;**4b:**4’-methyl;**4c:**5’-methyl;**4d:**6’-methyl

The coupling reaction of benzoic acid and nicotinic acid hydrazides with N protected L-amino acids including valine, leucine, phenylalanine, glutamic acid and tyrosine is reported. The target compounds, N-Boc-amino acid-(N`-benzoyl)- and NBoc (or *t*-butyloxycarbonyl)-amino acid-(N`-nicotinoyl) hydrazides **5a-5e** and **6a-6e** were prepared and purity using N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methyl-methanaminium hexafluorophosphate N-oxide (HATU) as coupling reagent. The antimicrobial activity of the Cu and Cd complexes of the designed compounds was tested. The products were deprotected affording the corresponding amino acid-(N`-benzoyl) hydrazide hydrochloride salts (**7a-7e**) and amino acid-(N`-nicotinoyl) hydrazide hydrochloride salts (**8a-8e**). These compounds and their Cu and Cd complexes were also tested for their antimicrobial activity. Several compounds showed comparable activity to that of ampicillin against *S. aureus* and *E. coli* [21]. The reaction of benzoic acid hydrazide (**3**) with different N-Boc-L-amino acids in dimethylformamide in the presence of triethylamine (Et_3N) as a base and N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-yl-methyl-ene]-N-methylmethanaminium hexafluorophsphate N-oxide (HATU) as coupling reagent at 0°C gave the compounds **5a-5e**. Similarly, nicotinic acid hydrazide was reacted with the same N-Boc-L-amino acids to give the compounds **6a-6e**. Compounds **5** and **6** were subjected to N-deprotection. The latter series upon deprotection of Boc group afforded the new series of compounds **7** and **8**. Compounds **5**, **6**, **7** and **8** were allowed to undergo complexation with Cu and Cd. All complexes were obtained by reacting one equivalent of the ligands **5**, **6**, **7** or **8** once with 2 equivalents of $Cu(NO_3)_2$ and once with 2 equivalents of $Cd(CH_3COO)_2$ in methanol. The Cu and Cd complexes were later decomposed and their Cu and Cd contents were analyzed by atomic absorption to

determine the ratio of complex formation of Cu and Cd to ligand. The atomic absorption analysis showed the formation of complexes Cu:L and Cd:L in the ratio (1:1).



X = CH; **5;** X = N; **6**



X = CH; **7;** X = N; **8**

a, R = $CH(CH_3)_2$; **b**, R = CH_2-CH_2-COOBn; **c**, R = CH_2-$CH(CH_3)_2$; **d**, R = CH_2-Ph; **e**, R = CH_2-[4-(OBn)C_6H_4].

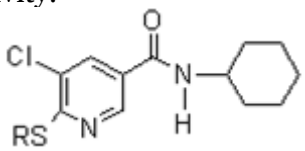
The compounds **5, 6, 7** and **8** and their **Cu** and **Cd** complexes have been evaluated for their antimicrobial activity. The MIC values listed in Table 1 show that all the test compounds have lower antifungal activity than clotrimazole.

Table 1: Minimal inhibitory concentration (MIC) of test compounds in μg/mL

Compound	E. coli	S. aureus	C. albicans	**Compound**	E. coli	S. aureus	C. albicans
Ampicillin	25	12.5	---------	(Cu:L),(1:1) of **6e**	100	**12.5**	200
Clotrimazole	------	-------	12.5	(Cd:L),(1:1) of **5a**	100	>200	>200
5a	>200	>200	>200	(Cd:L),(1:1) of **5b**	>200	**25**	>200
5b	>200	>200	>200	(Cd:L),(1:1) of **5c**	>200	>200	>200
5c	100	100	>200	(Cd:L),(1:1) of **5d**	>200	**25**	>200
5d	**50**	>200	>200	(Cd:L),(1:1) of **5e**	>200	>200	>200
5e	>200	>200	>200	(Cd:L),(1:1) of **6a**	>200	>200	>200
6a	>200	>200	>200	(Cd:L),(1:1) of **6b**	>200	100	>200
6b	**100**	>200	>200	(Cd:L),(1:1) of **6c**	100	>200	>200
6c	**50**	>200	>200	(Cd:L),(1:1) of **6d**	>200	>200	>200
6d	100	>200	>200	(Cd:L),(1:1) of **6e**	100	>200	>200
6e	**50**	>200	>200	(Cu:L),(1:1) of **7a**	>200	>200	>200
7a	100	**100**	>200	(Cu:L),(1:1) of **7b**	>200	>200	>200
7b	**25**	>200	>200	(Cu:L),(1:1) of **7c**	>200	100	>200
7c	100	50	>200	(Cu:L),(1:1) of **7d**	>200	50	>200
7d	100	>200	>200	(Cu:L),(1:1) of **7e**	>200	50	>200
7e	200	50	>200	(Cu:L),(1:1) of **8a**	>200	>200	>200
8a	**25**	>200	>200	**(**Cu:L),(1:1) of **8b**	>200	>200	>200
8b	100	100	>200	(Cu:L),(1:1) of **8c**	>200	>200	>200
8c	**50**	>200	>200	(Cu:L),(1:1) of **8d**	100	>200	>200
8d	100	100	>200	(Cu:L),(1:1) of **8e**	>200	**100**	>200
8e	**50**	100	>200	(Cd:L),(1:1) of **7a**	100	>200	>200
(Cu:L),(1:1) of **5a**	200	100	>200	(Cd:L),(1:1) of **7b**	>200	>200	>200
(Cu:L),(1:1) of **5b**	>200	>200	100	(Cd:L),(1:1) of **7c**	100	**12.5**	>200
(Cu:L),(1:1) of **5c**	100	50	>200	(Cd:L),(1:1) of **7d**	**50**	>200	>200
(Cu:L),(1:1) of **5d**	>200	50	>200	(Cd:L),(1:1) of **7e**	>200	>200	>200
(Cu:L),(1:1) of **5e**	200	**25**	>200	(Cd:L),(1:1) of **8a**	>200	>200	>200
(Cu:L),(1:1) of **6a**	>200	100	>200	(Cd:L),(1:1) of **8b**	100	>200	>200
(Cu:L),(1:1) of **6b**	>200	>200	>200	(Cd:L),(1:1) of **8c**	>200	>200	>200
(Cu:L),(1:1) of **6c**	>200	>200	>200	(Cd:L),(1:1) of **8d**	100	>200	>200
(Cu:L),(1:1) of **6d**	200	100	>200	(Cd:L),(1:1) of **8e**	>200	>200	>200

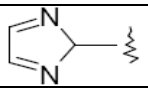
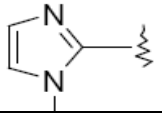
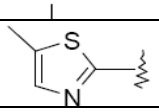
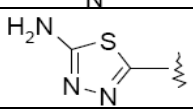
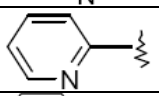
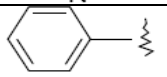
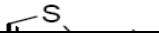
The test compounds are more active against *S. aureus* and *E. coli*. Compounds **(Cu:L),(1:1)** of **6e** and **(Cd:L),(1:1)** of **7c** have antimicrobial activity against *S. aureus* comparable to that of

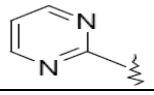
ampicillin, while the activity of compounds **(Cu:L),(1:1)** of **5e**, **(Cd:L),(1:1)** of **5b** and **(Cd:L),(1:1)** of **5d** is about 50% of that of ampicillin. Compounds **7b** and **8a** have antimicrobial activity against *E. coli* comparable to that of ampicillin, while the activity of compounds **5d**, **6c**, **6e**, **8c**, **8e**, **(Cd:L),(1:1)** of **7d** is about 50% of that of ampicillin. The utilized test organisms were: *E. coli* as an example of Gram-negative bacteria, *S. aureus* as an example of Gram-positive bacteria and *C. albicans* as yeast-like fungi. Ampicillin trihydrate and clotrimazole were used as standard antibacterial and antifungal agents, respectively. Solutions of the test compounds, ampicillin trihydrate and clotrimazole were prepared in DMSO to a concentration of 1600 µg/mL. Two fold dilutions of the compounds were prepared (800, 400 to 6.25µg/mL). Microorganism suspensions at 106 CFU/mL (Colony Forming Unit/mL) concentrations were inoculated to the corresponding wells. At the end of the incubation period, the MIC were determined [21]. The 5-chloro-N-cyclohexyl-6-thio substituted-nicotinamide derivatives **(9a-h)** has been performed against gram positive and gram-negative bacteria. The compound **9c** has found excellent antibacterial activity [22]. The 5,6-dichloro nicotinoyl chloride was treated with cyclohexylamine. The antibacterial activity of all the compounds **(9a-h)** has been performed against gram positive and gram-negative bacteria. Test solution and streptomycin having concentration 40 mg/ml and 20 mg/ml were prepared in DMF. The inhibition zone for each test solution was measured in mm. The compounds were tested for their antibacterial activity against *E. Coli*, *S.Typhi*. *Streptococcus mutans* and *S. aureus* using streptomycin as standard drug. The biological activity of these compounds have been evaluated by filter paper disc method. The zone of inhibition are presented in Table 2. Compound **9c** were found to be more active against *S. aureus*, *S. mutans E. coli*. The compound **9c** is found to be more active against *S. aureus*, *E. coli* and *S. mutants*. The influence of methyl group in 4th position of thiazole ring of compound **9c** showed good activity compared to other synthesized compounds. From this it can be concluded that the methyl group at 4th position may be responsible for good antibacterial activity.



9a-h

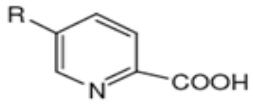
Table 2: Antibacterial activity of 5-Choloro-N-Cyclohexyl-6-thio substituted nicotinamide derivatives 9a-9h

Compound	R	Concentration (mg/ml)	Zone of Inhibition in mm*			
			Gram +ve		Gram –ve	
			S. aureus	*S. Typhi*	*S. mutans*	*E. coli*
9a		20	11	10	11	-
		40	11	15	12	15
9b		20	10	10	10	18
		40	14	12	12	23
9c		20	16	15	18	-
		40	22	15	22	23
9d		20	10	10	8	10
		40	--	10	11	12
9e		20	10	12	12	10
		40	12	16	15	12
9f		20	11	14	12	13
		40	12	15	14	15
9g		20	13	10	12	11

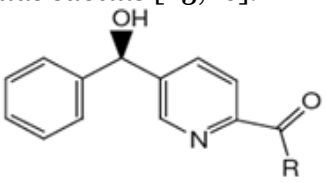
		40	14	12	13	13
9h		20	10	12	11	10
		40	11	13	12	11
Streptomycin		20	18	18	16	16
		40	---	22	20	22

** Average of three determinations*

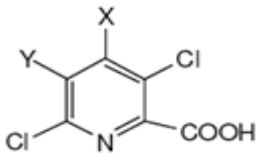
Vertilecanin C, a natural product and [methyl 2-(3-benzoylpicolinamido)acetate], 2 new phenyl-substituted derivatives of vertilecanin A were synthesized. Vertilecanin A type phenopicolinic acid derivatives were synthesized starting from nicotinic acid [23]. Picolinic acid and its derivatives are known as important organic compounds for humans and animals. Picolinic acid (**10**) itself plays a significant role in carrying metal ions in the human body and in animals. Calcium, magnesium, and potassium salts of picolinic acid are used as food and beverage supplements to improve the nutritive capacity of food stuffs and beverages [24]. 5-Alkylpicolinic acids **11-14**, which are known as hypotensive agents, are reported to have strong inhibitory effects on dopamine *β*-hydroxylase. Phenopicolinic acid **15**, originallyi solated from cultures of a *Paecilomyces* sp., is a dopamine *β*-hydroxylase inhibitor and shows antihypertensive activity. Halogen-containing picolinic acids **16, 17** have been widely used as herbicides in agriculture and are potential contaminants of ground water [25]. The need for new sources of environmentallyfr iendly pesticides and fungi displaying a 'broad spectrum' of parasitic abilities has been increasing. Isolated 5 new fungal metabolites were vertilecanins **19-22**, from solid–substrate fermentation cultures of *Verticillium lecanii*. While **19-22** did not have insecticidal or antifungal activity, the most abundant component, vertilecanin A (**10**), displayed insecticidal activity against *Helicoverpa zea* and showed antibacterial activity against *Bacillus subtilis* [23,26].



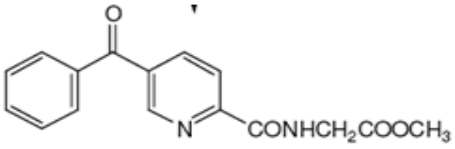
10 R=H, Picolonic acid; **11** R=CH_3; **12** R= C_2H_5; **13** R= iso-Propyl; **14** R= nButyl, fusaric acid; **15** R= p-Hydroxybenzyl, phenopicolinic acis



9 R=OH, Vertilecanin A; **10** R=OCH_3; **11** R=$NHCH_2CO_2H$, Verrtilecanin B; **12** R=$NHCH_2CO_2CH_3$

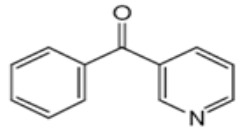


7 X=Y=H, Clopyralid; **8** X=NH2, Y=Cl, Picloram

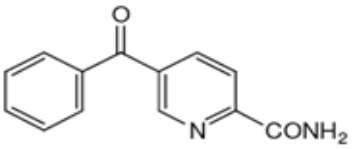


Vertilecanin C (**13**)

The preparation of vertilecanin A starting from nicotinic acid in 4 steps (Tumer, et al., 2005). The first synthetic preparation of vertilecanin C and 2 phenyl-substituted derivatives of vertilecanin A.



3-benzoylpyridine (**15**)



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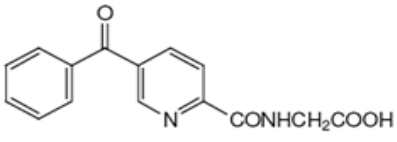

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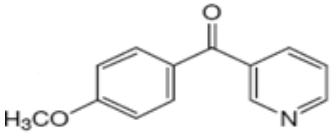

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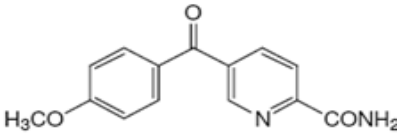

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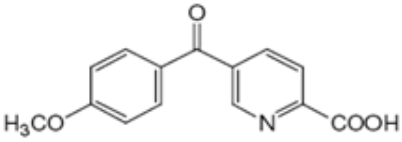

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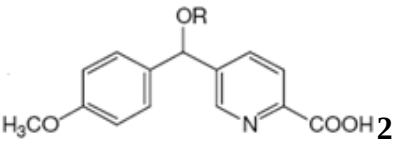
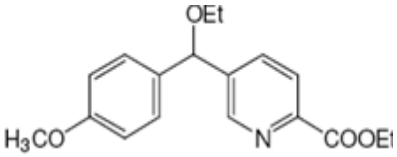


1 R= H; 22 R= C_2H_5 **2**



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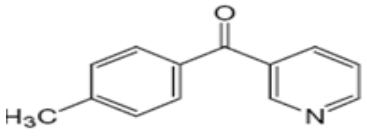

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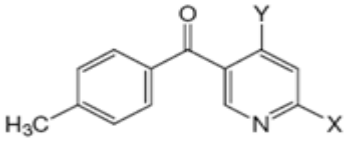
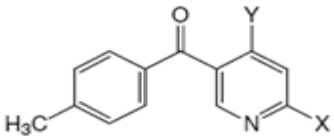
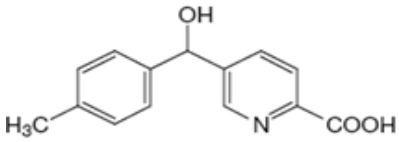


25; X=CONH2, Y=H**; 26;** X=H, Y=CONH2



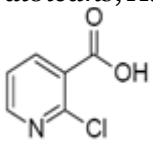
27; X=COOH, Y=H; **28;** X=H, Y=COOH



29

The synthesis of 2 new phenyl substituted analogues of vertilecanin A, which can be used for further chemical and biological purposes.

The compounds **35a–j**, 2-[(6-methyl-1,3-benzothiazol-2-yl)amino]-*N*- [2-(substituted phenyl/ furan-2-yl)-4-oxo-1,3-thiazolidin-3-yl]nicotinamides, were prepared from 2-chloropyridine-3-carboxylic acid **30** and 2-amino-6-methylbenzothiazole **31**. The *in vitro* antimicrobial screening of the compounds were carried out against two Gram positive (*S.aureus*, *S. pyogenes*), two Gram negative (*E. coli*, *P. aeruginosa*) bacteria and three fungal species (*C. albicans*, *A. niger*, *A. clavatus*). Some of the compounds are comparable with standard drugs [27].



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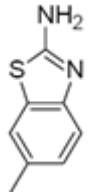

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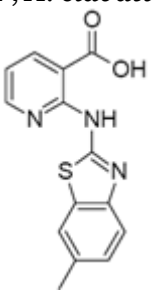

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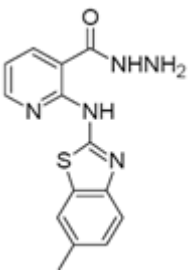

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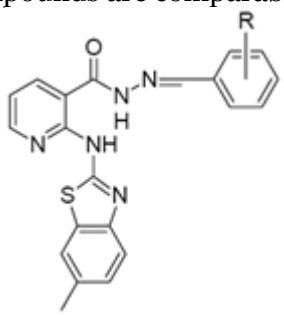
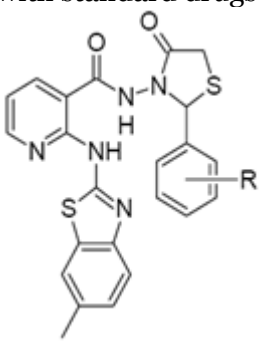


34a-j



35a-j

a: R=H; **b**: R=2-Cl; **c**: R=4-Cl; **d**: R=2-NO_2; **e**: R=3-NO2; **f**: R= 4-OH; **g**: R=4-OMe; **h**: R=3-OMe-4-OH; **i**: R=3-OMe-4-OH-5-NO_2; **j**: R=2-furyl

The 4-thiazolidinones incorporated nicotinic acid with 2-amino-6-methylbenzothiazole and examined their antimicrobial activities.

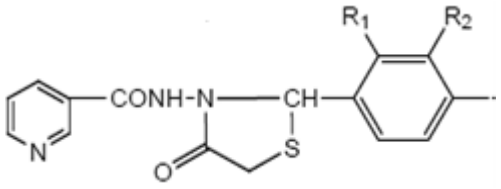
The *in vitro* antibacterial and antifungal activities of the compounds are shown in Table 3. The MICs (μg/ml) were carried out by broth microdilution method. *Antibacterial Activity:* It is evident that compound **30** displayed good to moderate activity against all bacteria (150–250 μg/ml). 2-Amino-6-methylbenzothiazole (**31**), compound **32** and hydrazide **33** exhibited moderate to poor activity against all bacteria. The result shows that compounds **34a**, **34e**, **34j**, **35d**, **35g** and **35j** exhibited good activity (25-100 μg/ml) against *E. coli*; **34d**, **34j**, **35d**, **35i** and **35j** exhibited good activity (50-100 μg/ml) against *P. aeruginosa*; **34a**, **35e**, **34f**, **34h**, **34j**, **35d**, **35b** and **35j** showed good to very good activity (25-150 μg/ml) against *S. aureus*; whereas **34b**, **34h**, **34j**, **35c**, **35i** and **35j** showed good activity (62.5-100 μg/ml) against *S. pyogenes* compared with ampicillin. All other compounds showed moderate activity. *Antifungal Activity:* From the results of the antifungal activity (Table 3), it is evident that compounds **30, 31, 32** and **33** showed good to moderate activity against *C. albicans*. Results also show that Schiff bases and 4-thiazolidinones possessed good activity against *C. albicans* while moderate activity against *A. niger* and *A. clavatus*. Compounds **34a**, **34d**, **34g**, **34j**, **35b**, **35e**, **35f** and **35j** showed better activity (100-500 μg/ml) against *C. albicans* when compared with griseofulvin, while all compounds showed poor to moderate activity against *A. niger* and *A. clavatus* [27].

Table 3: Antibacterial and antifungal activities of **34a–j** and **35a–j**

Compound	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram negative		Gram positive				
	E. coli	*P. aerug.*	*S. aureus*	*S. pyogenus*	*C .albicans*	*A. niger*	*A. clavatus*
30	150	150	200	250	250	500	500
31	250	125	500	1000	1000	1000	1000
32	500	1000	500	1000	500	250	250
33	500	500	150	200	250	1000	1000
34a	100	500	150	200	100	500	500
34b	500	500	500	100	1000	1000	>1000
34c	500	500	1000	1000	1000	>1000	>1000
34d	250	62.5	500	500	250	1000	1000
34e	62.5	150	100	200	1000	500	500
34f	200	250	150	250	1000	1000	1000
34g	250	500	500	1000	150	500	500
34h	200	200	62.5	62.5	>1000	>1000	>1000
34i	500	500	500	500	>1000	500	>1000
34j	25	50	50	62.5	100	500	500
35a	250	250	500	500	1000	1000	1000
35b	500	500	150	500	150	1000	1000
35c	500	1000	1000	100	>1000	>1000	>1000
35d	50	100	100	150	>1000	1000	500
35e	250	250	500	500	500	>1000	>1000
35f	250	250	500	500	250	500	>1000
35g	62.5	200	500	500	1000	>1000	500
35h	200	500	500	500	1000	1000	1000
35i	500	100	1000	100	>1000	500	>1000
35j	100	62.5	25	100	500	1000	1000
Ampicillin	100	100	250	100	–	–	–
Griseofulvin	–	–	–	–	500	100	100

Most of the compounds are comparable with ampicillin. Compounds bearing –Cl, $–NO_2$ groups and furan nucleus are more active than the remaining compounds. Compounds **34a**, **34d**, **34g**, **34j**, **35b**, **35e**, **35f** and **35j** were found to be active against *C. albicans* but they found poor with other fungal species. All the compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* against two Gram positive *S. aureus*, *S. pyogenes* and two Gram negative *E. coli*, *P. aeruginosa* bacteria and three fungal species *C. albicans*, *A. niger* and *A. clavatus*. Ampicillin was used for antibacterial activity while griseofulvin for antifungal activity were used as a standard drug [28-29].

Six compounds of thiazolidinone derivatives of nicotinic acid were evaluated *in vitro* antibacterial and antifungal activities (Table 4). The MIC of the compounds was also determined. Significant antimicrobial activities were observed for some compounds of the series. Some of them showed comparable activity as that of the standard drug used [30].

Compounds	Structure	R_1	R_2	R_3
36a		H	H	H
36b		OH	H	H
36c		H	H	Cl
36d		H	H	OCH_3
36e		H	OCH_3	OH
36f		H	OH	H

The *in vitro* antibacterial and antifungal activities of the compounds were evaluated at 25µg/ml, 50µg/ml and 75µg/ml concentration. Ciprofloxacin 50µg/ml and Ketaconazole 50µg/ml were used as standard. DMSO was used as solvent control. The MIC of the compounds were also determined. The antibacterial activity of the synthesized compounds was tested against *Staphylococcus aureus*, *S. epidermidis*, *Klebsiella pneumonia* and *Escherichia coli* using nutrient agar medium. The antifungal activity of the compounds was tested against *Candida albicans* and *Aspergillus niger* using sabouraud dextrose agar medium.

Table 4: Antimicrobial activity of compounds **36a-36f**

Compound	Zone of inhibition (mm)						MIC (µg/disc)					
	Antibacterial activity†				Antifungal activity†		Antibacterial activity†				Antifungal activity†	
	S.A.	***S.E.***	***K.P.***	***E.C.***	***A.N.***	***C.A.***	***S.A.***	***S.E.***	***K.P.***	***E.C.***	***A.N.***	***C.A.***
36a	+	+	+ +	+ +	+++	++	+	++	+	+	+	+
36b	++	++	+++	++	+++	++	+	+	+	+	+	+
36c	++	++	++	++	+++	++	+	++	+	+	+	+
36d	++	++	+++	+++	++	++	+	+	+	+	+	+
36e	+	+ +	++	+	+++	++	+	+	+	++	+	+
36f	++	++	++	+	++	++	+	+	++	+	+	+
C.P.	+++	+++	++++	++++	-	-						
K.C.	-	-	-	-	++++	+++						
C.	-	-	-	-	-	-						

S.A.-*Staphylococcus aureus*; S.E.-*Staphylococcus epidermidis*; K.P. -*Klebsiella pneumonia*; E.C.-*Escherichia coli*; A.N. -*Aspergillus niger*; C.A.-*Candida albicans*; C.P.- Ciprofloxacin (50 µg/ml); K.C.-Ketaconazole (50 µg/ml); C- Control; Concentration of the compounds: 50 µg/ml; Zone of inhibition: 10-15 mm = +; 16-20 mm = ++; 21-25 mm = +++ and 25 < = ++++.

All these compounds were evaluated for *in vitro* antibacterial and significant antifungal activities. Among the compounds, compounds **36b** and **36d** pocess significant activity against bacterial organisms whereas **36c** showed very less activity. Other compounds showed moderate antibacterial activity. Compounds **36c** and **36e**, showed Zone of inhibition (for 50µg/ml) and MIC of the synthesized compounds have been summarized in Table 4 [30]).

Discussion

Nicotinic acid derivatives are reported to show variety of biological activities. Nicotinic acid which belongs to water soluble vitamin B complex is also indicated is hyperlipidemia to lower triglycerides and cholesterol [31]. Keeping in view the importance of the above heteryl nuclei and considering the scope to introduce nicotinoyl moiety into heterocyclic compounds it was thought worthwhile to undertake the synthesis of the titled compounds. Nicotinic acid compounds exhibited a significant activity when compared with reference drugs. It suggests that they may be selectively targeted to *Mtb* growth, also considering that they were not cytotoxic to host cells at the same concentration and could be a good start point to find new lead compounds. More information about structure-activity relationship and their antibacterial activity test are in progress. A series of compound were synthesized with the presumption of estimating its anti-microbial property. The title compounds possess moderate to good anti-microbial potency, However auxiliary studies is desired to wrap up anything distinct about the therapeutic potential of these compounds. The nicotinic acid derivatives and its metal complexes were showed interesting results comparable to ampicillin. The uncomplexed compounds showed higher antimicrobial activity against *E. coli* compared to their respective complexes. While the complexes showed higher antimicrobial activity against *S. aureus* compared to their respective ligands. A large number of drugs and biologically relevant molecules contain heterocyclic systems. Often the presence of hetero atoms or groupings imparts preferential specificities in their biological responses. The chemistry and biological study of heterocyclic compounds has been interesting field for a long time due to medicinal and agricultural reasons. The number of heterocyclic derivatives containing nitrogen and sulfur atom

possess broad spectrum of biological activities. One of the most important heterocycle in medicinal chemistry is pyridine with wide application including antimicrobial, anti-inflammatory, anti-HIV, antiplasmodial, anti-tubercular, antibacterial and anticonvulsant [32-36] activities, and has much other important biological significance. Importance of hetero cyclic compounds has long recognized in the field of synthetic organic chemistry. It is well known that heterocyclic compounds containing nitrogen and sulphur exhibit a wide variety of biological activity. A series of pyridine derivative were evaluated for antitumor activities [37]. Nicotinamide has been shown to be beneficial in the treatment of papular and pustular acne, as well as improvement of skin cancer [38]. Nicotinamide or nicotinic acid has been used to treat diseases such as hypercholesterolemid and schizophrenia [39]. Nicotinamide and its derivatives are also used to prevent type-1 diabetes in animal model and humans showed cytotoxic properties [40,41]. On the other hand 6–chloro–3-substituted pyridine are very important class of heterocycles and are widely used in pharmaceutical and agrochemical industry [42,44]. The increasing interest in the chemistry of nicotinamide and its substituted derivatives result from the wide possibilities and their practical application for obtaining biologically active agents. Derivatives of Sprotected triazole and diazole exhibit high anti-inflammatory activity [45] Interest is to search antibacterial activity of S-protected derivatives of nicotinamide. An attempt has been made to understand the antibacterial behavior of these compounds *in vitro* [46] (Cutshall, et al., 2001).

Conclusion

In general, nicotinic acid derivatives are showed different types of biological properties. These compounds showed extensive variety of biological special property. In present study, some nicotinic acid derivatives are evaluated as anti-microbial properties. The result of the anti-bacterial activity evaluation proved to be significant with respect to the reference drugs. Some compounds exhibited potent anti-microbial activity. Nicotinic acid derivatives were synthesized with the belief of estimating its anti-microbial possessions. These compounds possess reasonable to fine anti-microbial effectiveness. It suggests that this class of compounds may be selectively targeted to *Mtb* growth, also considering that they were not cytotoxic to host cells at the same concentration and could be a good starting point to find new lead compounds.

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