Available online on 25.12.2017 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

SYNTHESIS AND ANTIMICROBIAL SCREENING OF SOME IMIDAZOLIDINE DERIVATIVES OF ISONICOTINAMIDE

Rakesh Patel[1], Pritesh Paliwal[1], Anil Bhandari[2]

[1] Indore Institute of Pharmacy, Indore (MP), India

[2] Goenka College of Pharmacy, Lachhmangarh, Sikar (Raj) India

E-mail address: patelcip@gmail.com

ABSTRACT

New series of *N* (2-alkyl/aryl-5-oxo-imidazolidine-1-yl) isonicotinamide derivatives were synthesized by the reaction of Schiff base with amino acetic acid in the presence of 1:4 dioxane. Synthesized compounds were evaluated for their Anti-bacterial activity against *Staphylococcus aureus* and *Echerichia coli*, Antifungal activity against *Candida Albicans* and Anti-tubercular activity against *Mycobacterium tuberculosis*. Synthesized compounds show significant activity against bacterial, fungal and mycobacterium strains. Their structures were established on the basis of elemental analysis, IR, ^{1}H NMR and Mass Spectral data.

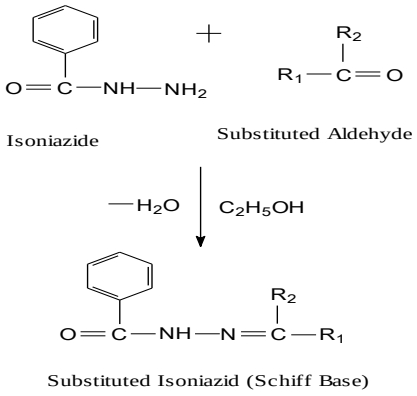
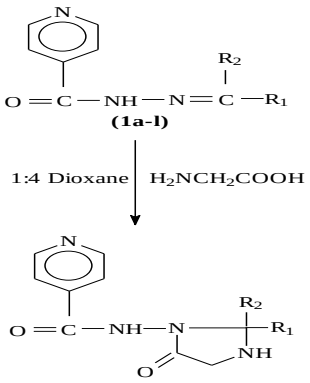
Cite this article as: Patel R, Paliwal P, Bhandari A, Synthesis and antimicrobial screening of some imidazolidine derivatives of isonicotinamide , Journal of Drug Delivery and Therapeutics. 2017; 7(7):150-153

INTRODUCTION:

Antimicrobial agents act against microbial organisms and inhibit their growth and reproduction. Antibiotics and antimicrobial term used synonymously but there is a difference between both the terms. Antibiotic refers to substances produced by microorganisms that act against another microorganism where antimicrobial agent may be synthetic. Thus, antibiotics do not include antimicrobial substances that are synthetic (sulfonamides and quinolones), or semisynthetic (methicillin and amoxicillin), or those which come from plants (quercetin and alkaloids) or animals (lysozyme)[1]. Microbial infection is the major cause of death in the world, although deaths from bacterial and fungal infection have dropped currently. Natural, synthetic and semi synthetic antimicrobial agents have been used since a long time against the life threatening infectious diseases [2]. Although deaths from bacterial and fungal infection have dropped currently, still those are the major cause of death in the world. Over the few past decades the bacterial resistance to antibiotics, anti-fungal and anti-tuberculotic drugs has become one of the most challenging problem in the infections treatments. Tuberculosis (TB) is the world's oldest known infectious disease that kills three million deaths each year[3].

MATERIAL AND METHOD:

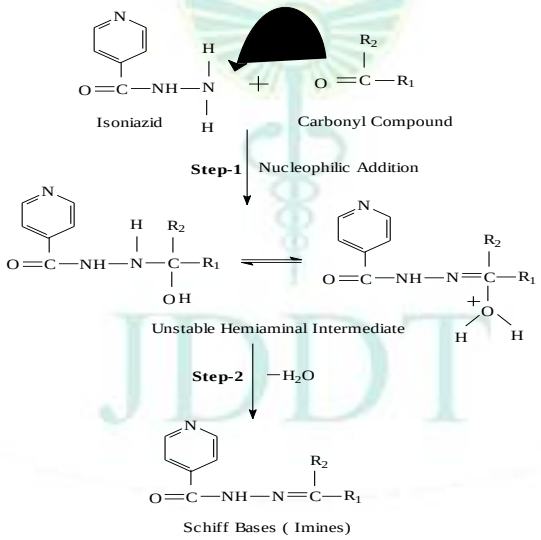
All the chemicals used were purchased from E Merck, S D Fine and Loba Chem and were purified by established methods (whenever needed). Various Substituted Isoniazid (Schiff Base) derivatives were prepared according to the procedure outline in scheme-I. imidazolidine derivatives were synthesized by formation of imines (from Schiff base) and ketenes (from amino acetic acid) followed by cycloaddition of ketenes to imines, in the presence of 1:4 Dioxane, in a single step reaction. Melting points were determined by open capillary tube method and are uncorrected. Purity of synthesized compounds was checked by TLC plates (Silica Gel G) and visualized by iodine vapor. The infra red absorption spectra of the synthesized compounds were recorded using KBr disc on FTIR 8010 Shimadzu model. 1H NMR spectra were recorded on Brucker Spectrospin DPX 300 spectrophotometer. Mass spectra were recorded on Jeol SR-102 FAB Mass spectrometer. CHN analyses of synthesized compounds were done on Perkin-Elmer-240 analyzer[4].

1(a-f)	N (2-alkyl/aryl-5-oxo-imidazolidine-1-yl) isonicotinamide (2a-f)
	
Part A: Synthesis of various Schiff Bases by the reaction of isoniazid with substituted aldehydes	**Part B:** Synthesis of N-(5-oxo-2-alkyl/aryl imidazolidine-1-yl) isonicotinamide derivatives

Mechanism of reactions involved in synthesis of titled compounds

Part A: It involves synthesis Schiff Bases by the reaction of isoniazid and substituted carbonyl compounds which proceeds in two steps; 1) Nucleophilic addition forming unstable hemiaminal intermediates and 2) Hemiaminal intermediate formation followed by dehydration to form Schiff Bases (imines).

Part B: This part of synthesis of titled compounds is attributed to synthesis of N-(5-oxo-2-alkyl/aryl-imidazolidine-1-yl) isonicotinamide derivatives, 2 (a-f)



The stepwise reaction mechanism is as follows:

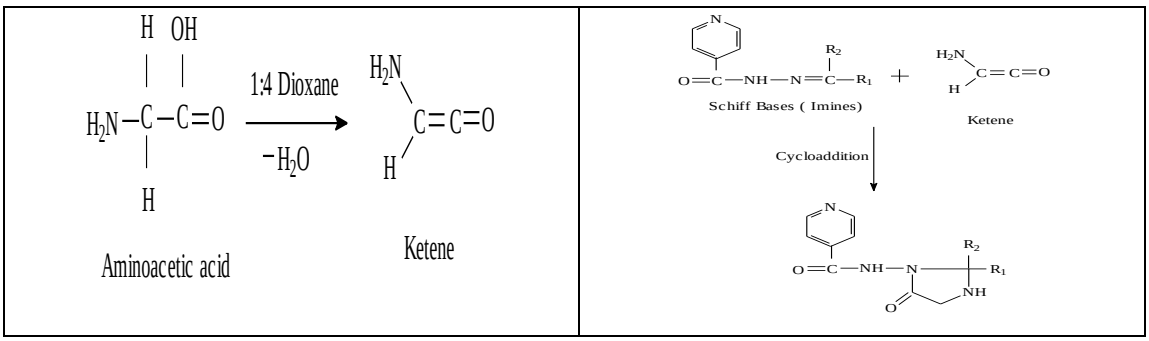
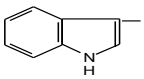


Table 1: Physical Characteristics of synthesized compounds:

Comp.	R_1	R_2	Molecular Weight	Yield (%)	Melting Point (°C)	Rf Value
2a	CH_3	C_6H_5	296.32	1.95gm (65.88%)	215-7	0.7
2b	C_6H_5	C_6H_5	358.39	2.46gm (68.72%)	242-4	0.7
2c		H	272.26	1.56gm (57.35%)	276-8	0.7
2d		H	283.29	1.74gm (61.48%)	275-7	0.5
2e		H	321.33	2.17gm (67.60%)	276-8	0.8
2f		H	288.33	1.83gm (63.54%)	244-6	0.8

General Procedure for Synthesis of substituted isoniazid, (Schiff Base) 1(a-f):

In a round bottomed flask, isoniazid (0.1mol), substituted aldehyde (0.1mol) and ethanol (30-35 ml) was taken and refluxed for three hours. The solution was cooled at room temperature and allowed to stand for 5 hours. Solid product was separated out, filtered, washed with ice cooled distilled water, dried and recrystalised with ethanol.

General procedure for synthesis of N-(2-mehtyl-5-oxo-imidazolidine-1-yl)isonicotinamide, 2(a-f)

0.01 mol of substituted isoniazid 1(a-f) (Schiff Base) and amino acetic acid (0.75gm, 0.01 mol) was dissolved in 1:4 dioxane (25ml) with constant stirring. The content was transferred to round bottom flask and heated under reflux for 5 hours. The mixture was allowed to cool at room temperature. The solid product was filtered, washed with ice cold water, dried and recrystalised from ethanol.

Compound 2a: IR (KBr, Cm^{-1}) 3390 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3040 (Aromatic -C-H Stre.), 1660 (C-N Stre pyridine ring), 1610 (acyclic C=O stre.), 1490 (CH_2 bend.), 1420 (CH_3), 1340 (C-NH imidazolidine). H^1 NMR (DMSO-d_6 δ ppm): 9.6 (m, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.8 (m, 4H, CH pyridine), 7.2 (m, 5H, aromatic H), 3.3 (d, 2H, -CH_2- aromatic), 2.2 (s, 3H, CH_3). Mass Peaks: 296.7 (M^+), 219.5, 204.7, 121.1, 84.7, 78.1. Elemental analysis% found: C-64.85%, H-5.44 %, N-17.69%

Compound 2b: IR (KBr, Cm^{-1}) 3390 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3050 (Aromatic -C-H Stre.), 1660 (C-N Stre pyridine ring), 1610 (acyclic C=O stre.), 1490 (CH_2 bend.), 1340 (C-NH imidazolidine). H^1 NMR (DMSO-d_6 δ ppm): 9.6 (m, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.8 (m, 4H, CH pyridine), 6.9-7.6 Mass Peaks: 358.7 (M^+), 281.5, 204.7, 121.1, 84.7, 78.1. Elemental analysis% found: C-70.31%, H5.06 %, N-15.62%

Compound 2c: IR (KBr, Cm^{-1}) 3390 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3050 (Aromatic -C-H Stre.), 1660 (C-N Stre pyridine ring), 1610 (acyclic C=O stre.), 1490 (CH_2 bend.), 1420 (CH_3), 1340 (C-NH imidazolidine), 1310 (cyclic C-O Stre). H^1 NMR (DMSO-d_6 δ ppm):9.6 (1H NH cyclic), 8.1 (1H, NH amide), 7.6-7.8 (4H, CH pyridine), 5.8 (3H furfural), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-). Mass Peaks: 272.3 (M^+), 205.8, 121.1, 84.7, 78.1. Elemental analysis% found: C-57.35%, H 4.44 %, N-20.58%

Compound 2d: IR (KBr, Cm^{-1}) 3390 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3050 (Aromatic -C-H Stre.), 1660 (C-N Stre pyridine ring), 1610 (acyclic C=O stre.), 1490 (CH_2 bend.), 1420 (CH_3), 1340 (C-NH imidazolidine). H^1 NMR (DMSO-d_6 δ ppm) 9.6 (1H NH cyclic), 8.1 (1H, NH amide), 7.6-7.8 (8H, CH pyridine), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-). Mass Peaks: 283.4 (M^+), 205.8, 121.1, 84.7, 78.1. Elemental analysis% found: C-59.36%, H 4.63 %, N-24.72%

Compound 2e: IR (KBr, Cm^{-1}) 3390 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3050 (Aromatic -C-H Stre.), 1660 (C-N Stre pyridine ring), 1610 (acyclic C=O stre.), 1490 (CH_2 bend.), 1420 (CH_3), 1340 (C-NH imidazolidine), 790 (N-H wag). H^1 NMR (DMSO-d_6 δ ppm) 9.6 (1H NH cyclic), 8.1 (1H, NH amide), 7.7-7.8 (4H, CH pyridine), 7.6 (4H, CH benzene), 7.2 (1H NH indole), 6.4 (1H, CH pyrole), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-). Mass Peaks: 321.2 (M^+), 205.7, 121.1, 84.7, 78.1. Elemental analysis% found: C-63.54%, H 4.71%, N-21.79%

Compound 2f: IR (KBr, Cm^{-1}) 3390 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3050 (Aromatic -C-H Stre.), 1660 (C-N Stre pyridine ring), 1610 (acyclic C=O stre.), 1490 (CH_2 bend.), 1420 (CH_3), 1350 (C-NH imidazolidine), 1310 (C-S Stre). H^1 NMR (DMSO-d_6 δ ppm) 9.6 (1H NH cyclic), 8.1 (1H, NH amide), 7.7-7.8 (4H, CH pyridine), 7.2-7.3 (3H, CH thiophene), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-). Mass Peaks: 288.5 (M^+), 205.8, 121.1, 84.7,

78.1. Elemental analysis% found: C-54.15%, H 4.20%, N-19.43%

Antimicrobial Activity All the synthesized compounds were evaluated for their invitro antimicrobial activity against gram positive bacteria *staphylococcus aureus* (ATCC-24392), the gram negative bacteria *Echerichia coli* (ATCC-24391) in nutrient agar media, fungi *C Albicans* (ATCC-436) in sabouraud dextrose medium and *mycobacterium tuberculosis* (ATTC-27286) in tween-albumin medium. The zone of inhibition values were determined and compared with well known (standard) antibacterial (Ofloxacin), antifungal (Ketoconazole) and antituberculotic (Isoniazid) drugs. Table: 2 shows data obtained from the biological screening of synthesized compounds and reference drugs.

Table 2: Antimicrobial screening data of compounds 2a-2f.

Compounds	Zone of Inhibition (in mm) at concentration of 20 µg/mL)			
	S. aureus	***E. Coli***	***C. Albicans***	***M. tuberculosis***
2a	17	19	23	28
2b	18	19	24	31
2c	19	20	32	32
2d	23	22	28	29
2e	25	27	31	34
2f	19	19	27	31
Ofloxacin	17	19	-----	-----
Ketoconazole	-----	-----	25	-----
Isoniazid	-----	-----	-----	28

RESULTS AND DISCUSSION:

Yield of synthesized compounds were found to be satisfactory. The purity of synthesized compounds and completion of reactions were checked by TLC on silica Gel G plates in the solvent system methyl chloride: methanol (8:2 v/v) and visualized spots in iodine vapor. Proposed structures were confirmed by Spectral and microanalysis data. IR spectra showed presences of various functional groups that were further supported by the H^1 NMR and Mass spectral data. Furthermore elemental analysis data were also found in agreement with calculated values from proposed structures. Antibacterial, antifungal and anti tuberculotic screening data of synthesized compounds showed good to moderate activity as compared to reference drug. Compound 2c and 2d showed moderate and 2b, and 2e showed good activity against tested strains. Amongst these compounds 2e showed best antibacterial, antifungal and anti tuberculotic activity against all strains. The antimicrobial potency of synthesized compounds is due the presence of pharmacological active isonicotinamide moiety and increased by the addition of imidazolidine moiety.

CONCLUSION:

On the basis of above research work; the results and discussion showed that the synthesized compounds showed good antimicrobial activity as compared to reference antimicrobial drugs. These results concluded the need of development of such type of compounds in future for the progress of drug synthesis area.

REFERENCES:

1. Patel R, Bhandari A, Synthesis and antimicrobial screening of some. N-(4-oxo-2-alkyl/aryl-thiazolidine-3-yl) isonicotinamide derivatives, Der Pharmacia Sinica, 2016, 7, 28-33.
2. Patel R, Bhandari A, Synthesis and antimicrobial screening of some thiazolidine derivatives of isoniazid, Der Chemica Sinica, 2016, 7, 8-13.
3. Patel R, Bhandari A, Synthesis and Antimicrobial Screening of Some 4-Substituted-3-Chloro-2-Oxo-Azetidine Derivatives, Asian J Res Chem, 2014, 7, 950-953.
4. Ramuz H, 1981 U S Patent No. 4244957.