Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2016, 7(2):8-13

Der Chemica Sinica
Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and antimicrobial screening of some thiazolidine derivatives of isoniazid

***Rakesh Patel[1] and Anil Bhandari[2]**

[1]*Indore Institute of Pharmacy, Indore (MP) India*
[2]*Goenka Collage of Pharmacy, Lachhmangarh, Sikar (Raj) India*

ABSTRACT

Some new N-(4-oxo-2-alkyl/aryl-thiazolidine-3-3yl) isonicotinamide derivatives of isoniazid have been synthesized and evaluated for their Anti-bacterial, Antifungal and Anti-tubercular activity. Synthesized compounds show significant activity against bacterial, fungal and mycobacterium strains. Their structures were established on the basis of elemental analysis, IR, 1H NMR and Mass Spectral data.

Keywords: INZ, Isoniazid, Thiazolidine, Anti-mycobacterial, TB

INTRODUCTION

The word antimicrobial was derived from the Greek words anti (against), mikros (little) and bios (life) and refers to all agents that act against microbial organisms. This is not synonymous with antibiotics, a similar term derived from the Greek word anti (against) and biotikos (concerning life). By strict definition, the word "antibiotic" refers to substances produced by microorganisms that act against another microorganism. 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).

Microbial infection is the major cause of death in the world, although deaths from bacterial and fungal infection have dropped currently [1]. Natural, synthetic and semi synthetic antimicrobial agents have been used since a long time against the life threatening infectious diseases[2]. 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. The urgency to develop new and effective drugs is due to the resistance development by strains against current medications and grooving problem of co-infection in immunocompromised patients [3-4].

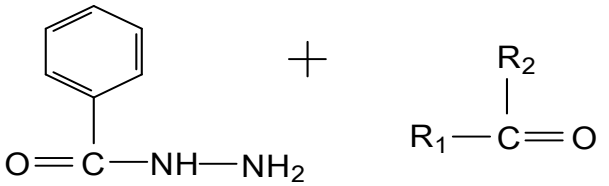
Several research has been done and currently in progress to develop new and better chemical entity against infections. Literature survey reveals that 2-oxo-azetidines have shown various biological activities along with antimicrobial activity [4-26]. In view of these findings some thiazolidine derivatives of Isoniazid have been synthesized and evaluated for Anti-bacterial, Antifungal and Anti-tubercular activity.

MATERIALS AND METHODS

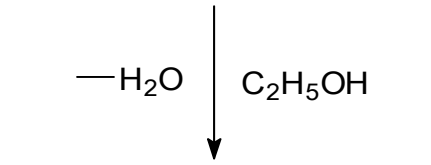
All the chemicals used were purchased from E Merk, S D Fine and Loba Chem and were purified by established methods (whenever needed). Various Substituted Isoniazid (Schiff Base) derivatives and N-(4-oxo-2-alkyl/aryl-thiazolidine-3-yl) isonicotinamide derivatives were prepared according to the procedure outline in scheme-I and Scheme-II respectively. 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. ^{1}H 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.

Part A: Synthesis of various Schiff Bases by the reaction of isoniazid with substituted aldehydes, **1(a-f)**
Synthetic Scheme-I:



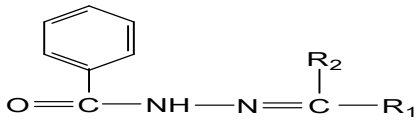
Isoniazide Substituted Aldehyde



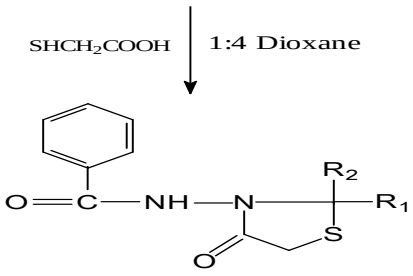
Substituted Isoniazid (Schiff Base)

Part B: Synthesis of N-(4-oxo-2-alkyl/aryl-thiazolidine-3-yl) isonicotinamide derivatives, 2 (a-f)

Synthetic Scheme-II:

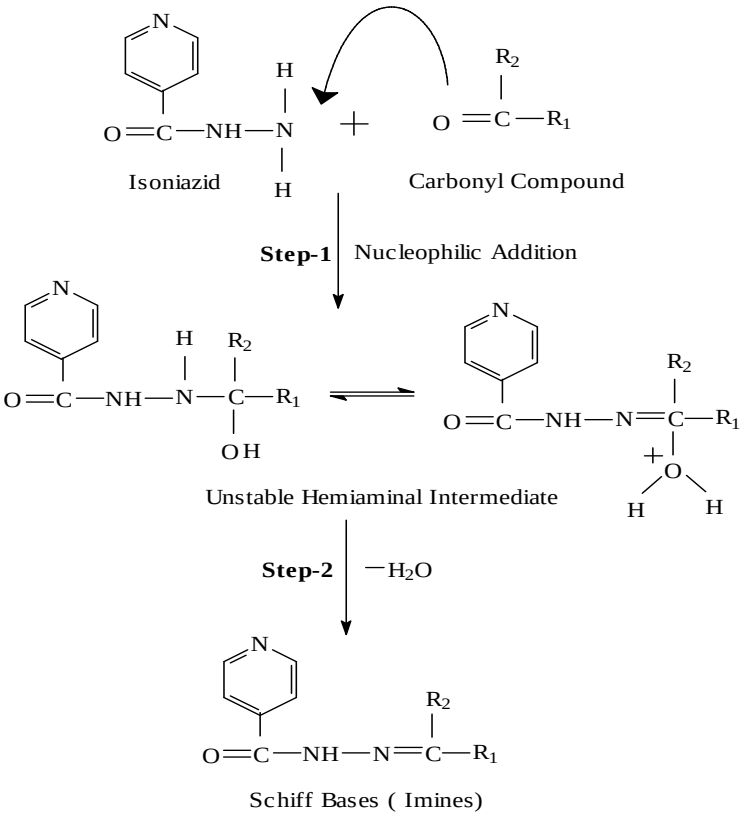


Substituted Isoniazid (Schiff Base)

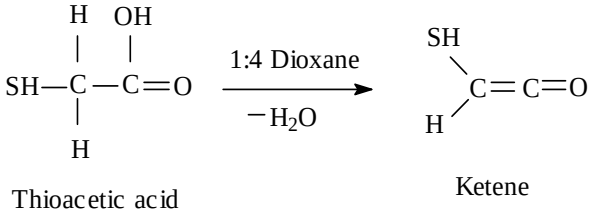


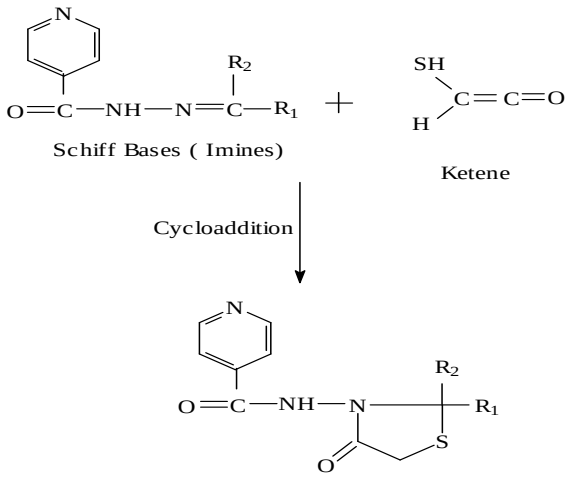
N-(4-oxo-2-alkyl/aryl-thiazolidine-3-yl) isonicotinamide derivatives, 2 (a-f)

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).



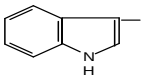
Part B: This part of synthesis of titled compounds **(2a-f)** is carried via formation of ketene followed by cycloaddition reaction as follow:





N-(4-oxo-2-alkyl/aryl-thiazolidine-3-yl) isonicotinamide derivatives, **2 (a-f)**

Table: 1 Physical properties of synthesized compounds

Comp.	R_1	R_2	Molecular Formula	Molecular Weight	Yield (%)	Melting Point (°C)	Rf Value
2a	CH_3	C_6H_5	$C_{16}H_{15}N_3O_2S$	313.37	68.37	265-7	0.7
2b	C_6H_5	C_6H_5	$C_{21}H_{17}N_3O_2S$	375.44	62.67	254-6	0.7
2c		H	$C_{13}H_{11}N_3O_3S$	289.31	61.59	244-6	0.5
2d		H	$C_{14}H_{12}N_4O_2S$	300.34	55.33	262-4	0.8
2e		H	$C_{17}H_{14}N_4O_2S$	338.38	62.72	284-6	0.7
2f		H	$C_{13}H_{11}N_3O_2S_2$	305.38	59.67	275-7	0.4

General Procedure for Synthesis of substituted isoniazid, (Schiff Base) 1(a-f):
In a round bottomed flask, isoniazid (0.1mol), substituted aldehyde (0.1 mol) 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 recristallised with ethanol.

General procedure for Synthesis of N-(4-oxo-2-alkyl/aryl-thiazolidine-3-yl) isonicotinamide derivatives 2(a-f):
0.01 mol of substituted isoniazid 1(a-l) (Schiff Base) were dissolved in 25ml of 1:4 dioxane with constant stirring. Thioglycolic acid (1ml) was added slowly dropwise with stirring. The content was transferred to round bottom flask and heated under reflux for 8 hours. The mixture was allowed to cool and poured into aqueous solution of sodium bicarbonate to remove unreacted thioglycolic acid. The solid product was filtered, dried and recrystalised from ethanol.

Compound 2a: N-(2-methyl-2-phenyl-4-oxo-thiazolidine-3-yl) isonicotinamide:
IR (KBr, Cm^{-1}): 3460 (N-H Str. Secondary Amide), 3050 (Aromatic -C-H Str.), 1690 (C=O Str thiazolidine ring), 1640(C=N of pyridine), 1600 (acyclic C=O str.), 1490 (CH_2 bend.), 1410 (CH_3), 1370 (CH-N), 830 (-C-S-C), 800 (C-H Str Phenyl). H^1 NMR (DMSO-d_6 δ ppm): 8.1 (s, 1H, NH amide), 7.7-7.8 (m, 4H, CH pyridine), 7.2 (m, 5H, aromatic H), 3.3 (s, 2H, -CH_2- aromatic), 2.2 (s, 3H, CH_3). Mass Peaks: 313.1(M^+), 236.7, 222.4, 121.1, 116.1, 78.1. Elemental analysis% found (% calculated): C- 61.26 (61.32), H-4.68 (4.82) N- 13.18 (13.41).

Compound 2b: N-(2, 2-diphenyl-4-oxo- thiazolidine-3-yl) isonicotinamide:
IR (KBr, Cm^{-1}): 3460 (N-H Str. Secondary Amide), 3040 (Aromatic -C-H Str.), 1690 (C=O Str thiazolidine ring), 1640(C=N of pyridine), 1600 (acyclic C=O str.), 1490 (CH_2 bend.), 1370 (CH-N), 830 (-C-S-C), 810 (C-H Str Phenyl). H^1 NMR (DMSO-d_6 δ ppm): 8.1 (s, 1H, NH amide), 7.7-7.8 (m, 4H, CH pyridine), 6.9-7.4 (m, 10H, aromatic H), 3.3 (s, 2H, -CH_2- aromatic). Mass Peaks: 375.2 (M^+), 298.7, 222.4, 121.1, 116.1, 78.1. Elemental analysis% found (% calculated): C- 66.98 (67.18), H-4.68 (4.56) N- 13.18 (13.12).

Compound 2c: N-(2- furfural- 4-oxo- thiazolidine-3-yl) isonicotinamide:
IR (KBr, Cm^{-1}): 3460 (N-H Str. Secondary Amide), 3040 (Aromatic -C-H Str.), 1690 (C=O Str thiazolidine ring), 1640(C=N of pyridine), 1600 (acyclic C=O str.), 1490 (CH_2 bend.), 1300 (Aromatic C-O), 1370 (CH-N), 830 (-C-S-C), 810 (C-H Str Phenyl). H^1 NMR (DMSO-d_6 δ ppm): 8.1 (s, 1H, NH amide), 7.7-7.8 (m, 4H, CH pyridine), 5.8 (t, 3H, -CH furfural), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-). Mass Peaks: 289.4 (M^+), 222.4, 121.1, 116.1, 78.1. Elemental analysis% found (% calculated): C- 54.14 (53.97), H-3.42 (3.83) N- 14.14 (14.52).

Compound 2d: N-(4-oxo-2-pyridine- thiazolidine-3-yl) isonicotinamide:
IR (KBr, Cm^{-1}): 3460 (N-H Str. Secondary Amide), 3040 (Aromatic -C-H Str.), 1690 (C=O Str thiazolidine ring), 1640(C=N of pyridine), 1600 (acyclic C=O str.), 1490 (CH_2 bend.), 1370 (CH-N), 830 (-C-S-C), 810 (C-H Str Phenyl). H^1 NMR (DMSO-d_6 δ ppm): 8.1 (s, 1H, NH amide), 7.7-7.8 (m, 8H, CH pyridine), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-). Mass Peaks: 300.4 (M^+), 222.4, 121.1, 116.1, 78.1. Elemental analysis% found (% calculated): C- 56.16 (55.99), H-3.82 (4.03) N- 18.24 (18.65).

Compound 2e: N-(2-indole-4-oxo- thiazolidine-3-yl) isonicotinamide:
IR (KBr, Cm^{-1}): 3460 (N-H Str. Secondary Amide), 3040 (Aromatic -C-H Str.), 1690 (C=O Str thiazolidine ring), 1640(C=N of pyridine), 1600 (acyclic C=O str.), 1490 (CH_2 bend.), 1370 (CH-N), 830 (-C-S-C), 810 (C-H Str Phenyl), 770 (N-H wag). H^1 NMR (DMSO-d_6 δ ppm): 8.1 (s, 1H, NH amide), 7.7-7.8 (m, 4H, CH pyridine), 7.6 (m, 5H, CH indole), 7.2 (m, 1H, NH indole), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-). Mass Peaks: 338.9 (M^+), 222.4, 121.1, 116.1, 78.1. Elemental analysis% found (% calculated): C- 59.88 (60.34), H-3.96 (4.17) N- 16.68 (16.56).

Compound 2f: N-(4-oxo-2-thiophene- thiazolidine-3-yl) isonicotinamide:
IR (KBr, Cm^{-1}): 3460 (N-H Str. Secondary Amide), 3040 (Aromatic -C-H Str.), 1690 (C=O Str thiazolidine ring), 1640(C=N of pyridine), 1600 (acyclic C=O str.), 1490 (CH_2 bend.), 1370 (CH-N), 1320 (C-S Str thiophene), 830 (-C-S-C), 810 (C-H Str Phenyl). H^1 NMR (DMSO-d_6 δ ppm): 8.1 (s, 1H, NH amide), 7.7-7.8 (m, 4H, CH pyridine), 7.1-7.3 (t, 3H, CH thiophene), 3.3 (s, 2H, -CH_2- aromatic), 2.5 (s, 1H, aromatic –CH-). Mass Peaks: 305.5 (M^+), 222.4, 121.1, 116.1, 78.1. Elemental analysis% found (% calculated): C- 52.24 (51.13), H-3.38 (3.63) N- 13.56 (13.76).

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	14	15	23	28
2b	12	19	24	33
2c	17	19	26	35
2d	19	21	29	33
2e	16	23	32	35
2f	18	19	25	34
Ofloxacin	15	18	-----	-----
Ketoconazole	-----	-----	22	-----
Isoniazid	-----	-----	-----	31

RESULTS AND DISCUSSION

Chemistry:
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.

Antimicrobial Activity:
Antibacterial, antifungal and anti tuberculotic screening data of synthesized compounds showed good to moderate activity as compared to reference drug. Compound 2a, 2b and 2f showed moderate activity against all strains. Compound 2c, 2d, and 2e showed good antibacterial, antifungal and anti tuberculotic activity against tested strains. The antimicrobial potency of synthesized compounds is due the presence of pharmacological active isonicotinamide moiety and increased by the addition of thiazolidine.

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. Compound 2c showed better anti tuberculotic activity against tested strains. Compound 2e showed better antifungal and anti tuberculotic activity against tested strains. These results concluded the need of development of such type of compounds in future for the progress of drug synthesis area.

REFERENCES

[1] R. Patel, A. Bhandari, *American Journal of Advanced Drug Delivery* , **2014**, 2 [1], 104
[2] R. Patel, A. Bhandari, *Asian Journal of Research in Chemistry*, **2014**,7 (11), 950
[3] S. J. Gilani, S. A. Khan, O. Alam, N. Siddiqui, *Acta Poloniae Pharmaceutica-Drug Research*, **2011**, 68, 205
[4] K. D. Tripathi, Essentials of Medical Pharmacology, Japees Brothers Medical Publishers Pvt Ltd, New Delhi, **2003**
[5] D. A. William, T. L. Lemke, Foye's Principals of Medicinal Chemistry, *Lippincott Wiliams and Wilkins*, New York, **2002**
[6] A. Husain, *Acta Poloniae Pharmaceutica-Drug Research*, **2009**, 66, 513
[7] J. S. Gilani, A. S. Khan, A. Ozair, V. Singh and A. Arora, *J. Serb. Chem. Soc*. **2011**, 76 (8) 1057
[8] I.M. Gomez-Monterrey, P. Campiglia, O. Mazzoni, E. Novellino, M. V. Diurno *Tetrahedron Letters*, **2001**, 42, 5755
[9] X. Xu, X. Qian, Z. Li, G. Song, W. *Chen, Journal of Fluorine Chemistry*,**2004**, 125, 1159
[10] R. Markovic, A. Rasovic, M. Baranac, M. Stojanovic, P. J. Steel, S. Jovetic *J. Serb. Chem. Soc*. **2004**, 69 (11) 909
[11] A. S. Youssef, *World Journal of Chemistry* **2006**, 1 (1), 10
[12] T. Nazar, M. Dobosz, E. J. Wojtowicz, *Acta Poloniae Pharmaceutica - Drug Research*, **2007**, Vol. 64 (3) 227
[13] W. Jian-Quan, S. De-Long, T. Cheng-Xia, *Chin. J. Org. Chem*., **2007**, Vol. 27 (01) 126
[14] M. Mori, M. Takagi, C. Noritake, S. Kagabu, *J. Pestic. Sci*., **2008**, 33(4), 357
[15] G. M. A. Al-Sehemi, *JKAU: Sci.*, **2009**, Vol. 21 (1), 79
[16] L. Mosula, B. Zimenkovsky, D. Havrylyuk, A. V. Missir, I. C. Chirita, R. Lesyk Farmacia, , **2009**, Vol. 57 (3) 321
[17] I. Argyropoulou, A. Geronikaki, P. Vicini, F. Zanib, *ARKIVOC*-(vi), **2009**, 89
[18] C. K. R. Ganesh, D. B. Yadav, K B Venkatesh, *Indian Journal of Chemistry* **2010**, Vol 49B, 1151
[19] L. Srikanth, N. Raghunandan, P. Srinivas, A. G. Reddy, *Int. J. of Pharma and Bio Sci*., **2010**, Vol.1 (4) 120
[20] S. Ramachandran, P. Shanmugapandiyan, *IJPI's Journal of Medicinal Chemistry* **2010**, Vol 1 (1) 2
[21] H. A. Soleiman, *The Open Catalysis Journal*, **2011**, 4, 18
[22] S. Verma, S. K. Srivastava, P. Samadhiya, *IJPRD* **2011**, Vol 2 (11) 73.
[23] D. Prasad, A. Kumar, P. K. Shukla, M. Nath, *Organic and Medicinal Chemistry Letters* **2011**, 1(4) 1
[24] A. A. Zagade, G. P. Senthilkumar, *Der Pharma Chemica*, **2011**, 3(1), 523
[25] S. J. Gilani, S. A. Khan, O. Alam, V. Singh, A. Arora, *J. Serb. Chem. Soc*. **2011**, 76 (8) 1057
[26] L. Hong-xin, C. Xiao-tao, X. Liang-zhong, *Chem. Res. Chinese Universities*, **2011**, 27(3), 431