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SYNTHESIS & ANTI- MICROBIAL EVALUATION OF N-(2-(4-SUBSTITUTED PHENYL)-4-OXOTHIAZOLIDIN-3-YL) ISONICOTINAMIDE DERIVATIVES

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ABSTRACT

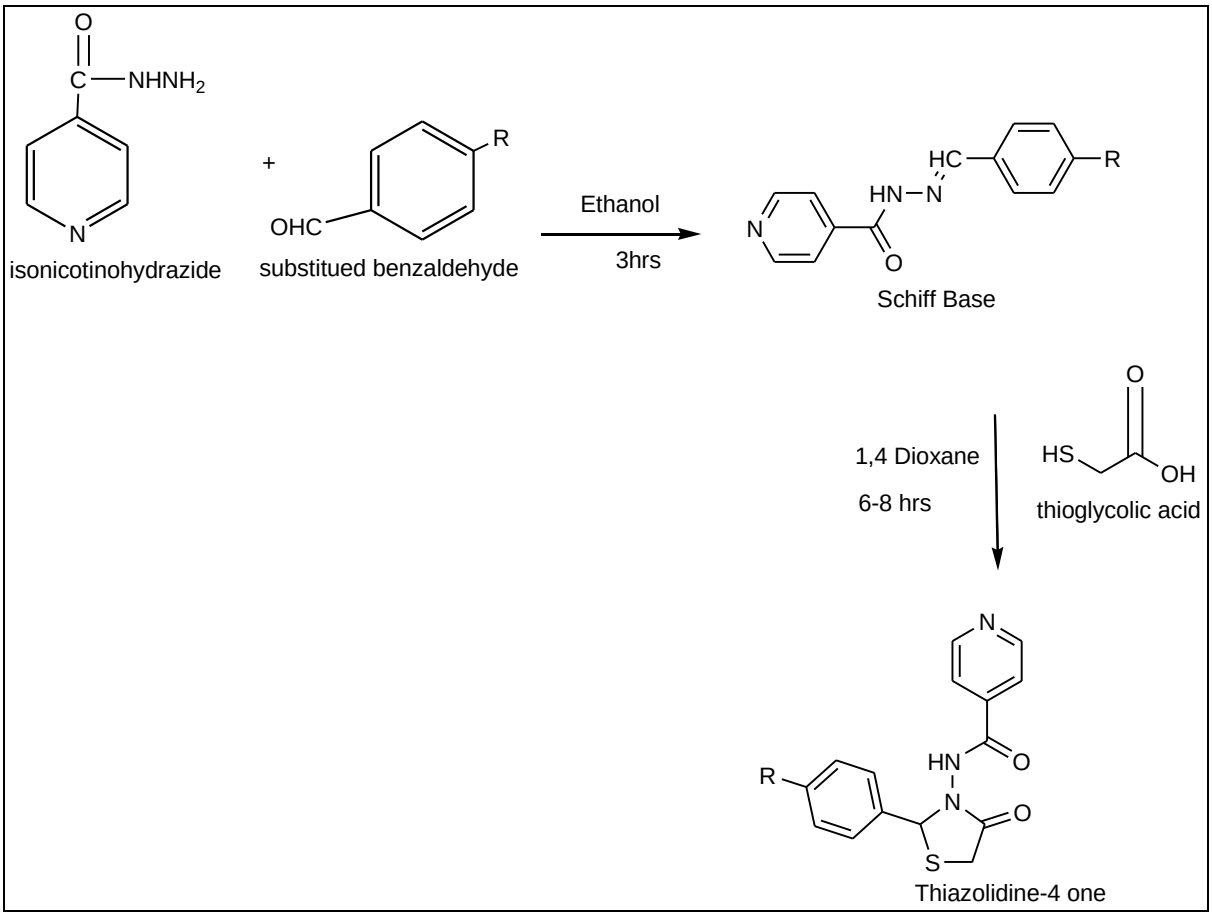
A new series N-(2-(4-substituted Phenyl)-4-oxothiazolidin-3-yl)isonicotin-amide of derivatives were synthesized by the reaction of Schiff base (isoniazid and substituted benzaldehyde) with mercaptoacetic acid. The chemical structures of the synthesized compounds were confirmed by means of IR, 1H-NMR. The synthesized compounds showed good antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

INTRODUCTION: Azetidinone and Thiazolidinone derivatives were reported to possess antibacterial [1-2], antifungal [1-2], antitubercular activity [3], anti-HIV [4], analgesic [5], anti inflammatory [5], and ulcerogenic activity [6]. Isoniazid derivatives were reported to possess antimicrobial [7] activities. Therefore it was envisaged that compounds containing both the chemical moieties would result in compounds of interesting biological activities. In this present study isoniazid were treated with different substituted aromatic aldehydes to produce Schiff's base [8]. The Schiff bases were subjected to addition reactions with thioglycolic acid in the presence of 1, 4-dioxane-anhydrous zinc chloride to produce 4-thiazolidinone derivatives [9]. The chemical structure of the synthesized compounds was confirmed by means of IR, 1H-NMR.

The synthesized compounds were screened for antibacterial (*Staphylococcus aureus, Escherichia coli)* by cup plate method.

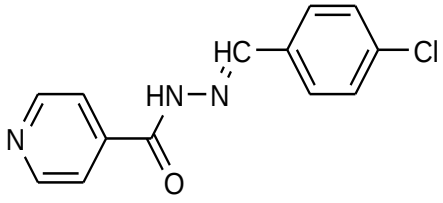
Chemistry: The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on Win-Bommen B-104 IR Spectrophotometer with KBr pellets. 1H-NMR spectra was recorded on Bruker- A VIII 500 MHz NMR Facility using DMSO-d6 as solvent. The chemical shifts are reported as parts per million downfield from tetramethylsilane (Me_4Si).

The purity of the compounds was checked by TLC on pre-coated aluminium sheets (Silica gel- 60 F254) using Chloroform: Glacial Acetic acid: water as mobile phase and visualized by iodine vapors.

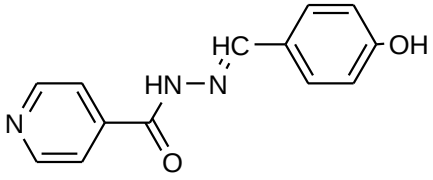


SYNTHETIC SCHEME

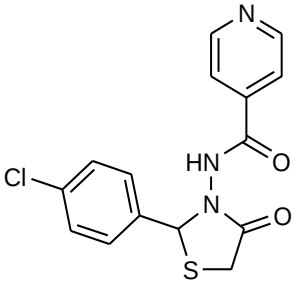
IVA- R= Cl, VA- R= OH, VIA- R= H, VIIA- R= $N(CH_3)_2$, IVB-R= Cl, VB- R= OH, VIB- R= H, VIIB- R= $N(CH_3)_2$



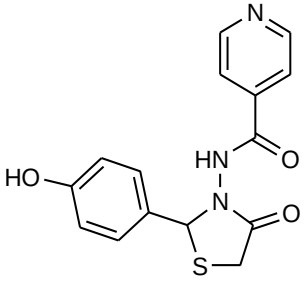
(*E*)-*N*'-(4-chlorobenzylidene)isonicotinohydrazide
Compound IV A



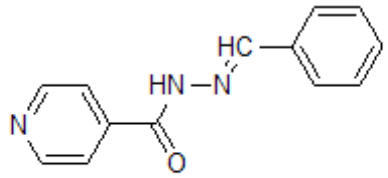
(*E*)-*N*'-(4-hydroxybenzylidene)isonicotinohydrazide
Compound Va



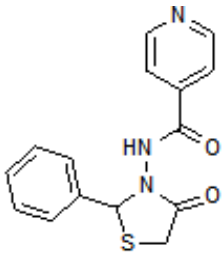
N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)isonicotinamide
Compound IV B



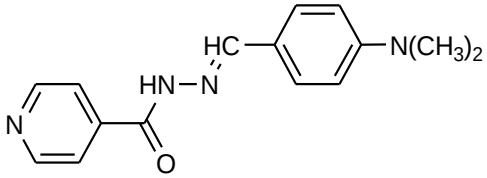
N-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)isonicotinamide
Compound Vb



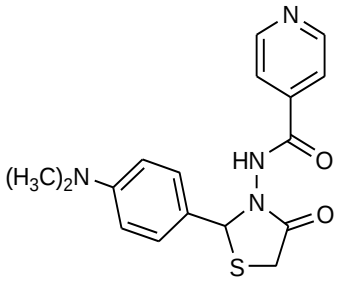
(*E*)-*N*'-benzylideneisonicotinohydrazide
Compound VI a



N-(4-oxo-2-phenylthiazolidin-3-yl)isonicotinamide
Compound VI b



(*E*)-*N*'-(4-(dimethylamino)benzylidene)isonicotinohydrazide
Compound VIIa



N-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)isonicotinamide
Compound VII b

General Methods of Synthesis of Schiff Bases (IVA, VA, VIA, VIIA): A mixture of Isoniazid 0.01mol), substituted benzaldehyde [10] (0.01mol) and a drop of acetic acid was dissolved in ethanol (25ml) and heated on a steam bath for 45-60 min or on a water bath for 2-3 hrs. The reaction mixture was allowed to stand at room temperature for 24hrs; the product separated out was filtered, dried under vacuum and recrystallized by using warm ethanol. The Schiff bases and thiazolidine-4-one derivatives were prepared by the method of S. Ramachandran *et al.*, [14].

IVA- (E)-N'-(4-chlorobenzylidene)isonicotinohydrazide

IR (KBr) cm^{-1}: 3452 (NH), 1667(C=O, Amide), 1596(C=N), 819(CH- Phenyl)

VA-(E)-N'-(4-hydroxybenzylidene)isonicotinohydrazide

IR (KBr) cm^{-1}: 3227(NH), 1658(C=O, Amide), 1597(C=N), 1285(C- OH)

VI A- (E)-N'-benzylideneisonicotinohydrazide

IR (KBr) cm^{-1}: 3024(NH), 1691(C=O, Amide), 1563(C=N), 845(CH- Phenyl)

VIIA-(E)-N'-(4-(dimethylamino)benzylidene)isonicotino hydrazide

IR (KBr) cm^{-1}: 3399(NH), 1665(C=O, Amide), 1590(C=N), 817(CH- Phenyl), 1311(N-methyl), 1428(CH_3)

General Methods of Synthesis of Thiazolidine-4-one (IVB, VB, VIB, VIIB): To a mixture of Schiff's base (0.01mol) and thioglycolic acid (0.01mol) dissolved in 1, 4 dioxane (20ml), anhydrous zinc chloride (0.004 mol) was added and refluxed for 8h. The reaction mixture was cooled, filtered, washed with water; vacuum dried and recrystallized using absolute ethanol.

IVB-N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)iso-nicotinamide

IR (KBr) cm^{-1}: 3464(NH), 1601(C=O amide), 1690(C=O), 1489(CH_2 Bending), 1371(CH-N)

1H-NMR

(DMSO-d6): 7.7-8.8(m; CH Pyridine), 7.5-7.6(m, CH benzene), 7.3(s, 1H; CH), 3.28(s, 2H; CH_2), 8.1(s; NH amide)

VB-N-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)iso-nicotinamide

IR (KBr) cm^{-1}: 1707(C=O), 1443(CH_2 Bending), 1596(C=O Amide), 1656 (C=O), 3229(NH), 1286, 3366(C-OH)

1H-NMR

(DMSO-d6): 7.1-7.8(m; CH Pyridine), 6.9-7.0(m, 1H; CH benzene), 5.9(s, 1H; CH), 4.0(s, 2H; CH_2), 5.1(s; aromatic OH), 8.1(s; NH amide)

VIB- N-(4-oxo-2-phenylthiazolidin-3-yl)isonicotinamide

IR (KBr) cm^{-1}: 3463(NH), 1672(C=O amide), 1689(C=O), 1489(CH_2 Bending), 1363(CH-N)

1H-NMR

(DMSO-d6): 7.8-8.8(m; CH Pyridine), 7.3-7.4(m, CH benzene), 5.2(s, 1H; CH), 3.5(s, 2H; CH_2), 8.4(s; NH amide)

VIIB- N-(2-(4-(dimethylamino) phenyl)-4-oxothiazolidin -3-yl)isonicotinamide

IR (KBr) cm^{-1}: 3432(NH), 1598(C=O, Amide), 1660(C=O), 1444(CH_2 Bending), 1305(N-methyl), 1420(CH_3), 1368 (CH-N).

1H-NMR

(DMSO-d6): 7.7-8.9(m; CH Pyridine), 6.7-6.8(m, CH benzene), 6.9(s, 1H; CH), 3.6(s; CH_2), 8.0(s; NH amide) 2.5(aromatic $N(CH_3)_2$)

Antimicrobial Activity: The antibacterial activity [11] of the synthesised compounds was tested against gram (+) bacteria (*Staphylococcus aureus* ATCC5144 *Bacillus cereus)* and gram (-) bacteria (*Escherichia coli* ATCC 25922 using Nutrient agar medium [11].

Cup Plate Method [12, 13]: Inoculate a previously liquefied medium appropriate to the assay with the requisite quantity of suspension of the micro organism, add the suspension to the medium at a temperature between 40 to 50°C and immediately pour the inoculated medium into petri dishes to give a depth of 3-4mm. Ensure that the layers of medium are uniform in thickness by placing the dishes or plates on a level surface.

The prepared dishes must be stored in a manner so as to ensure that no significant growth or death of the test organism occurs before the dishes are used and that the surface of the agar layer is dry at the time of use. The cavities in the agar plates are prepared be using a metal borer. The cavities formed must be uniform throughout the dish. Apply the solutions to the surface of the solid medium in sterile cavities prepared in the agar medium.

The volume of solution added to each cavity must be uniform and sufficient almost to fill those holes when these are used. Leave the dishes standing for 1-4 hrs at room temperature or at 4°C as appropriate as a period of pre-incubation diffusion to minimise the effects of variation in time between the applications of different solutions. Then the plates are incubated at 37±1°C for 24 hrs and observed for antibacterial activity. The diameter of the zone of inhibition was measured for the plates in which the zone of inhibition was observed.

The average area of inhibition was calculated and compared with that of the standards as shown in the **Table 1** below.

All the four compounds IVB, VB, VIB, VIIB that were synthesised were viewed for the antibacterial activity along with the standard ciprofloxacin 50µg/ml. Therefore, it instigated us to determine which synthesised compound has a good activity against both *Staphylococcus aureus* (Gram +ve) and *Escherichia coli* (Gram –ve) for a concentration of 500 µg/ml, as for 250 µg/ml there was no activity found out seeming that the lower concentration has no activity against both the organisms.

TABLE 1: COMPARISON OF ZONE OF INHIBITION OF ALL THE FOUR SYNTHESISED COMPOUND FOR THE CONCENTRATION OF 500 µg/ml FOR THE ANTIBACTERIAL ACTIVITY WITH *STAPHYLOCOCCUS AUREUS* (GRAM +VE) & *ESCHERICHIA COLI* (GRAM –VE)

Concentration of the compounds	*Staphylococcus aureus* (Gram +ve)				*Escherichia coli* (Gram –ve)			
	IVB	V B	VI B	VIIB	IVB	V B	VI B	VIIB
500 µg/ml	14mm	14mm	15mm	18mm	10mm	18mm	17mm	17mm
Standard Ciprofloxacin 50 µg/ml	30mm	30mm	30mm	30mm	30mm	30mm	30mm	30mm

SUMMARY AND CONCLUSION: The present work describes the synthesis of Schiff's bases and their thiazolidinone derivatives along with their antibacterial activities. The Schiff bases and thiazolidine- 4- one derivatives were prepared by the method of S. Ramachandran *et al*. The reaction completion was confirmed by TLC and the synthesised compounds were purified by recrystallization. The structures of the synthesised compounds were assigned on the basis of the spectral data.

The infra red, nuclear magnetic resonance spectra of these Schiff bases and thiazolidinone compounds showed the expected frequencies and signals.

The antimicrobial activity of the thiazolidinone derivatives was screened by the cup plate method for the standard drug, control and the sample. It showed that the compound had mild activity both towards gram +ve and gram –ve organism. The standard used was ciprofloxacin.

REFERENCE:

1. G. S. Singh, B. J. Molotsi, Synthesis of 2-azetidinones from 2-diazo-1, 2-diarylethanones and *N*-(2-thienylidene)imines as possible antimicrobial agents ,II Farmaco., 2005;60:727-730.
2. V. P. M. Rahman, S. Mukhtar, W. H. Ansari, G. Lemiere: Synthesis, stereochemistry and biological activity of some novel long alkyl chain substituted thiazolidin-4-ones and thiazan-4-one from 10-undecenoic acid hydrazide: Eur.J.Med.Chem, 2005; 40:173-184.
3. S. G. Kucukguzel, E. E. Orul, S. Rollas, F. Salin, A. Ozbek; Eur.J.Med.Chem., Synthesis, characterization and biological activity of novel 4-thiazolidinones, 1, 3, 4-oxadiazoles and some related compounds 2002; 37, 197-206.
4. R. K. Rawal, Y.S. Prabhakar, S. B. Katti, E. DeClercq; 2-(Aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT Inhibitors: Bioorg.Med.Chem., 2005; 13: 6771-6776.
5. M. G. Vigorita, R. Ottana, F. Monforte, R. Maccari, A. Trovato, M. T. Monforte, M. F. Taviano; Synthesis and anti-inflammatory, analgesic activity of 3, 3′-(1, 2-Ethanediyl)-bis[2-aryl-4-thiazolidinone] chiral compounds, Bioorg.Med. Chem. Lett. 2001; 11: 2791-2794.
6. B. Goel, T. Ram, R. Tyagi, E. Bansal, A. Kumar, D. Mukherjee, J.N.Sinha,2-Substituted-3-(4-bromo-2-carboxyphenyl)-5-methyl-4-thiazolidinones as potential anti-inflammatory agents, Eur.J.Med.Chem. 1999; 34:265-269.
7. K. P. Deepa, K. K. Aravindakshan, Synthesis, characterization, and antifungal studies of transition metal complexes of omega-bromoacetoacetanilide isonicotinylhydrazone, Appl Biochem Biotechnol. ;118 (1-3):283-92
8. M. Conli, R. Gulielmetli, J. Metzger; Synthesis, Physicochemical properties of Schiff's base in the benzothiazole series, Bull.Soc.Chim.Fr, 1967; 8: 2834-2841.
9. S. V. More, D. V. Dongarkhadekar, R. N. Chavan, W. N. Jadhav, S. R. Bhusare, R. P. Pawar. Synthesis and antibacterial activity of new Schiff bases, 4-thiazolidinones and 2-azetidinones, J.Indian.Chem.Soc. 2002; 79:768-769.
10. P. Shanmugapandiyan, A. Ramesh. Synthesis and antimicrobial activity of 1-(Benzothiazol-2'-yl)-5-phenyl-tetrazole, Organic chemistry – an Indian Journal, 2008; 1-8,.
11. S. H. Gillespie; .Medical Microbiology-Illustrated., Butterworth Heinemann Ltd., United Kingdom, 1994; 234- 247.
12. Bentley's textbook of Pharmaceutics, Eighth edition, 1996, 596-597.
13. Indian Pharmacopoeia, 1996; A-100,105.
14. S. Ramachandran and P. Shanmugapandiyan, Synthesis, characterisation, antimicrobial evaluation of Thiazolidine-4-one derivatives, IJPI"s Journal of Medicinal Chemistry, 2010; 1(1):1-6.

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