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Synthesis & Antimicrobial Activity of Thiazolidinone Derivatives

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ABSTRACT:

5-Arylidine derivatives of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) isonicotinamide are synthesized using three steps: synthesis of N-(4-chlorobenzylidene isonicotinohydrazide, synthesis of 4- thiazolidinone ring and finally synthesis of 5-benzilidene derivatives. A series of 5-arylidene derivatives of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) isonicotinamide have been synthesized using different typeS of substituted benzaldehyde and all synthesized compounds were screened for antibacterial and antifungal activities using the turbidimetric method. Turbidity produced is measured by taking absorbance and compared with turbidity produced by standard drug. Ciprofloxacin and clotrimazole were taken as the standard drugs for antibacterial activity and antifungal activity respectively. The compounds were screened against *E. Coli, B. Subtilis* and *S. Aureus* for antibacterial activity and against *Aspergillus niger*, C*andida albicans, S.cereviceaes* for antifungal activity. Penassay broth and Sabouraud broth medium were used for culturing bacterial and fungal strains respectively. Antibacterial screening revealed that most of the compounds showed activity and MIC was found to be 0.31 µg/ml. Antifungal screening revealed that most of the compounds showed activity and MIC was found to be 0.31 µg/ml aginst *Aspergillus niger*, *Candida albicans* and 0.15 µg/ml against S.*cereviceaes*.

KEY WORDS: Isoniazid, Thiazolidinone, Thiaglycolic acid, Antibacterial activity, Antifungal activity.

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INTRODUCTION:

For more than a century heterocyclic compounds rank against the most important organic compounds. They participate in important biochemical processes, and are the constituents of main substances (DNA, RNA) in living cells. It has been established that half of the therapeutic agents consist of heterocyclic compounds. The heterocyclic ring comprises the core of the active moiety or pharmacophore. Fungemia is an important cause of morbidity and mortality in hospitalized patients. Moreover, the emergence of resistance to currently available antifungals is of great concern and has led to susceptibility testing of new antifungal agents. The incidence of fungal infections have increased over the last two decades and Candida species were the predominant mycotic pathogen. Candida species produce broad range infections, ranging from superficial illness to life threatening disease[1].The importance of heterocyclic compounds has long been recognized in the field of synthetic organic chemistry. It is well known that a number of heterocyclic compounds containing nitrogen, oxygen and sulphur exhibit a wide variety of biological activity. Compounds carrying the thiazolidinone ring have been reported to demonstrate a wide range of pharmacological activities which include antimicrobial[2-12] antifungal activity[13], antitubercular[14], antitumor[15], antidiabetic activity[16,17]anti inflammatory[18,19], anticonvulsant[20].Thiazolidinone ring can be prepared by nucleophilic addition of thioglycolic/ thiolactic acid to C=N double bond. Hydrazide hydrazones obtained from the condensation reaction of hydrazides and aldehydes were treated with thioglycolic and thiolactic acid in anhydrous benzene.

MATERIAL AND METHOD:

5-Arylidine derivatives of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) isonicotinamide are synthesized using three steps: synthesis of isonicotinic acid hydrazide hydrazone, synthesis of 4- thiazolidinone ring and finally synthesis of 5-benzilidene derivatives. Melting points were determined by an open capillary method and are uncorrected. The completion of the reaction and purity of the compounds were checked by thin layer chromatography. IR spectra were recorded on Nicolet impact 400 FT/IR spectrometer using KBr pressed pellet technique. ^{1}HNMR spectra were recorded on GEOL-JMS D–300 (MHz) NMR spectrometer.

Synthesis of n-(4-chlorobenzylidene isonicotinohydrazide (1):

13.70 gm(0.1 M) isoniazid and 14.00 gm(0.1 M) p-chloro benzaldehyde were taken in 50 ml ethanol and then refluxed for half an hour. It was allowed to stand until room temperature is achieved and then poured into ice cold water and collected ppt and then recrystallized with C_2H_5OH, Yield 67.77%, Melting point 224-226°C; **IR (cm^{-1}, KBr):** 2900-3100 (C-H str. of aromatic) 1550 (C=C str of aromatic) 3250-3450 (N-H str of amide), 1650-1680 (C=O str amide), 1050-1088 (C-Cl str aryl chloride), 1590-

1610 (C=N str), 815-835(Para substitution); **^{1}HNMR, ppm (DMSO):** 7.55-7.64 (4H, m, aromatic proton), 8.47 (2H Ar-H proton near nitrogen of pyridine ring), 6.74 (2H Ar-H proton of pyridine ring), 8.31 (1H,CONH).

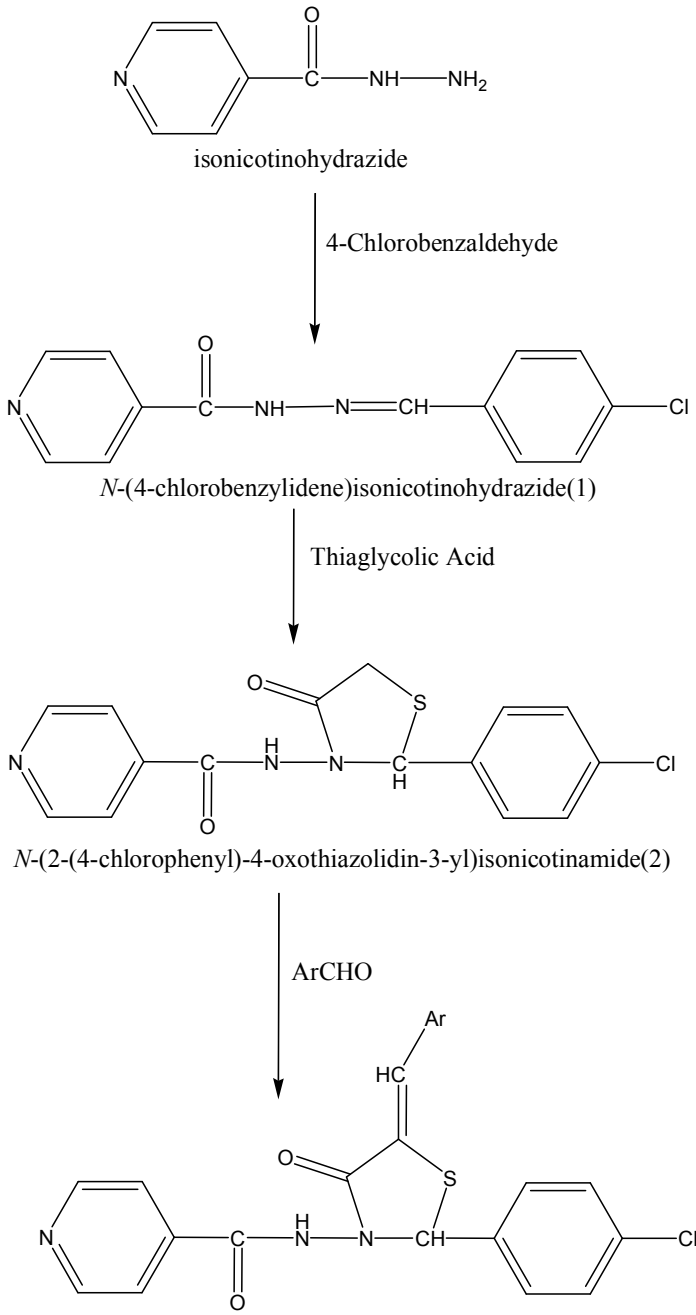

Figure1: Scheme of general synthesis

Synthesis of n-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) isonicotin- amide (2):

A mixture of (0.02 M) N-(4-chlorobenzylidene isonicotinohydrazide and required amount of thioglycolic acid (0.05 M) in DMF (80 ml), containing a pinch of anhydrous $ZnCl_2$ was refluxed for about 6 hrs. The reaction mixture was cooled and poured on to crushed ice. The solid thus obtained was filtered, washed with water and the product was recrystallized from rectified spirit. The purity of compound was checked by single spot TLC using ethyl aceate :acetone : methyl alcohol: water (5:2:2:1), Yield 67.77%, Melting point 188-190°C; **IR (cm^{-1}, KBr):** 2900-3100 (C-H str. of aromatic) 1550 (C=C str of aromatic) 3250-3450 (N-H str of amide), 1650-1680 (C=O str amide), 1050-1088 (C-Cl str aryl chloride), 1150-1185 (C-N str), 645-680(C-S-C str), 1590-1610 (C=N str), 815-835(Para substitution); **^{1}HNMR, ppm (DMSO):** 7.55-7.64 (4H, m, aromatic proton), 7.80 (1H, s, -SCHN), 8.47 (2H Ar-H proton near nitrogen of pyridine ring), 6.74 (2H Ar-H proton of pyridine ring), 8.31 (1H,CONH).

Synthesis of n-(5-benzylidene-2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) isonicotinamide (3a):

A mixture of (0.01M) of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) isonicotinamide and benzaldehyde (0.01 M) was refluxed in acetic acid (25 ml) in the presence of a anhydrous sodium acetate (0.01 M) for about 3-4 hrs. The mixture was cooled at room temperature and then poured into ice cold water. The solid separated was filtered and recrystallized from acetic acid to give benzilidene derivatives, Yield 37.89 %, Melting point 268-270°C; **IR (cm^{-1}, KBr**): 2900-3100 (C-H str. of aromatic) 1550 (C=C str of aromatic) 3250-3450 (N-H str of amide), 1650-1680 (C=O str amide), 1050-1088 (C-Cl str aryl chloride), 1150-1185 (C-N str), 645-680(C-S-C str), 1590-1610 (C=N str), 815-835(Para substitution) 880 (out of plane =CH bend)745(C-H_{def} Monosubstitution); **^{1}HNMR, ppm (DMSO):** 7.56 (5H, m, aromatic proton), 7.55-7.64 (4H, m, aromatic proton), 7.80 (1H, s, -SCHN), 8.48(2H Ar-H proton near nitrogen of pyridine ring), 6.76 (2H Ar-H proton of pyridine ring), 8.31 (1H,CONH), 6.73 (1H,=CH), 7.53 (1H,CH=C),

Synthesis of n-(2-(4-chlorophenyl)-5-(furan-2-ylmethylene)-4-oxo thia- zolidin-3-yl) isonicotinamide (3b):

A mixture of (0.01M) of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) isonicotinamide and furfuraldehyde (0.01M) was refluxed in acetic acid (25 ml) in the presence of a anhydrous sodium acetate0(.01 M) for about 3-4 hrs. The mixture was cooled at room temperature and then poured into ice cold water. The solid separated was filtered and recrystallized from acetic acid to give benzilidene

derivatives. Yield 32.77%, Melting point 254-255°C; **IR (cm^{-1}, KBr):** 2900-3100 (C-H str. of aromatic) 1550 (C=C str of aromatic) 3250-3450 (N-H str of amide), 1650-1680 (C=O str amide), 1050-1088 (C-Cl str aryl chloride), 1150-1185 (C-N str), 645-680(C-S-C str), 1590-1610 (C=N str), 815-835(Para substitution) 880 (out of plane =CH bend) 1170(C-O-O str); **^{1}HNMR, ppm (DMSO):** 7.53-7.64 (4H, m, aromatic proton), 7.68 (d,1H Ar-H proton furyl) 7.61(d,2H Ar-H proton of furyl) 7.80 (1H, s, -SCHN), 8.48 (2H Ar-H proton near nitrogen of pyridine ring), 6.76 (2H Ar-H proton of pyridine ring), 8.31 (1H,CONH), 6.73 (1H,=CH), 7.53 (1H,CH=C).

Synthesis of n-(5-(4-chlorobenzylidene)-2-(4-chlorophenyl)-4-oxothiazo idin-3-yl)isonicotinamide (3c):

A mixture of (0.01M) of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) isonicotinamide and 4-chlorobenzaldehyde (0.01 M) was refluxed in acetic acid (25 ml) in the presence of a anhydrous sodium acetate (0.01M) for about 3-4 hrs. The mixture was cooled at room temp. and then poured into ice cold water. The solid separated was filtered and recrystallized from acetic acid to give benzilidene derivatives, Yield 55.67%, Melting point 232-234°C; **IR (cm^{-1}, KBr):** 2900-3100 (C-H str. of aromatic) 1550 (C=C str of aromatic) 3250-3450 (N-H str of amide), 1650-1680 (C=O str amide), 1050-1088 (C-Cl str aryl chloride), 1150-1185 (C-N str), 645-680(C-S-C str), 1590-1610 (C=N str), 815-835(Para substitution) 880 (out of plane =CH bend); **^{1}HNMR, ppm (DMSO):** 7.51-7.64 (4H, m, aromatic proton), 7.87 (1H, s, -SCHN), 8.46(2H Ar-H proton near nitrogen of pyridine ring), 6.76 (2H Ar-H proton of pyridine ring), 8.31 (1H,CONH), 6.73 (1H,=CH), 7.53(1H,CH=C).

Synthesis of n-(5-(4-(dimethylamino)benzylidene)-2-(4-chlorophenyl)-4-oxo thiazolidin-3-yl) isonicotinamide (3d):

A mixture of (0.01M) of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) isonicotinamide and 4-dimethyl amino benzaldehyde (0.01 M) was refluxed in acetic acid (25 ml) in the presence of a anhydrous sodium acetate (0.01M) for about 3-4 hrs. The mixture was cooled at room temp. and then poured into ice cold water. The solid separated was filtered and recrystallized from acetic acid to give benzilidene derivatives, Yield 76.56 %, Melting point 262-264°C; **IR (cm^{-1}, KBr):** 2900-3100 (C-H str. of aromatic) 1550 (C=C str of aromatic) 3250-3450 (N-H str of amide), 1650-1680 (C=O str amide), 1050-1088 (C-Cl str aryl chloride), 1150-1185 (C-N str), 645-680(C-S-C str), 1590-1610 (C=N str), 815-835(Para substitution) 880 (out of plane =CH bend); **^{1}HNMR, ppm (DMSO):** 7.53-7.68 (4H, m, aromatic proton of Ar-Cl), 7.68-7.81 (4H aromatic proton of Ar-$N(CH_3)_{2)}$) 7.79 (d,2H Ar-H proton near $N(CH_3)_2$

) 7.81 (1H, s, -SCHN) 8.48(2H Ar-H proton near nitrogen of pyridine ring), 6.76(2H Ar-H proton of pyridine ring), 8.33 (1H,CONH),6.73 (1H,=CH), 7.53(1H,CH=C), 2.91-2.96 (6H,N(CH_3)$_2$).

Synthesis of n-(5-(2-nitrobenzylidene)-2-(4-chlorophenyl)-4-oxothiazol idi -3-yl) isonicotinamide (3e):

Isonicotinamide and 2-nitro benzaldehyde (0.01 M) was refluxed in acetic acid (25 ml) in the presence of a anhydrous sodium acetate (0.01M) for about 3-4 hrs. The mixture was cooled at room temp. and then poured into ice cold water; the solid separated was filtered and recrystallized from acetic acid to give benzilidene derivatives, Yield 45.62%, Melting point 237-239°C; **IR (cm^{-1}, KBr):** 2900-3100 (C-H str. of aromatic) 1550 (C=C str of aromatic) 3250-3450 (N-H str of amide), 1650-1680 (C=O str amide), 1050-1088 (C-Cl str aryl chloride), 1150-1185 (C-N str), 645-680 (C-S-C str), 1590-1610 (C=N str), 815-835(Para substitution) 880 (out of plane =CH bend) 1370 (Ar-NO_2str) 770 (meta substitution); **^{1}HNMR, ppm (DMSO):** 7.53-7.69 (4H, m, aromatic proton of Ar-Cl), 7.72-8.30 (4H aromatic proton of Ar-NO_2)) 8.10 (d,2H Ar-H proton near NO_2) 7.80 (1H, s, -SCHN), 8.30-8.74(2H Ar-H proton near nitrogen of pyridine ring), 6.73 (1H,=CH), 7.55 (1H,CH=C),.

EVALUATION OF ANTIMICROBIAL ACTIVITY:

All synthesized compounds were screened for antibacterial and antifungal activities using the Turbidimetric method and turbidity produced is measured by taking absorbance and compared with turbidity produced by standard drug. Penassay broth and Sabouraud broth medium were used for culturing bacterial and fungal strains respectively. Ciprofloxacin and Clotrimazole were used as a standard for comparison of the results.

Antibacterial activity:

Most of the compounds showed moderate antibacterial activity at low concentration against *E. coli, B. subtilis* and *S. aureus.* Against *E. coli* all most all the titled compounds were found to have activity. Compounds 3b, 3c and 3e were found to have better activity than other titled compounds. MIC of 3b, 3c, 3e was found to be 0.31 µg/ml. Against *S. aureus* all compounds were found to have activity while compound 3a, 3c and 3e were found to have good activity. MIC of 3a, 3c and 3e was found to be 0.31 µg/ml. Against *B. subtilis*, almost all compounds were found have activity but compounds 3c and 3e were found to have better activity. But none of the activity was comparable to the standard. MIC of 3c

and 3e was found to be 0.31 µg/ml. Antibacterial screening revealed that compounds exhibit moderate activity as compared to the standard.

Antifungal activity:

Against *A. niger* all compounds were found to have activity while Compound 3a, 3b, 3e were found to have good activity. MIC of 3a, 3b, 3e was found to be 0.31 µg/ml..Against *C. albicans*, almost all titled compounds were found to have good activity.MIC of compounds 3b and 3e were found to be 0.15 µg/ml. Against *S. cereviseae* all compounds were found to have activity while compound 3b and 3e were found to have good activity. MIC of compound 3b and 3e were found to be 0.31 µg/ml. .Antifungal screening revealed that compounds exhibit moderate activity as compared to the standard.

Table 1: Antibacterial activity (MIC of synthesized compound)

Compound No.	MIC range (µg/mL)		
	E. coli	*B. subtilus*	*S.aureus*
3a	1.25	1.25	0.62
3b	0.62	0.31	0.62
3c	0.31	1.25	0.31
3d	0.62	1.25	0.62
3e	0.31	0.62	0.31
Ciprofloxacin	0.15	0.25	0.01

Table 2: Antifungal activity (MIC of synthesized compound)

Compound No.	MIC range (µg/mL)		
	A. niger	*C. albicans*	*S.cereviseae*
3a	0.62	0.31	1.25
3b	0.62	0.15	0.62
3c	0.62	0.31	0.31
3d	0.62	0.62	0.31
3e	0.62	0.15	0.31
Clotrimazole	0.10	0.30	0.20

RESULT AND DISCUSSION:

A large number of 4-thiazolidinone derivatives have been reported to exhibit a number of activities like anti-inflammatory, analgesic, anti-hiv, local anesthetic, cytotoxic, antibacterial, and antifungal activity. Looking into these findings the compounds having this general structure were synthesized. All the synthesized 5-Arylidine derivatives of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) isonicotinamide were found to have antibacterial and antifungal activities. Antibacterial activity was done against two gram positive bacteria (S*taphylococcus aureus, Bacillus subtilis*) and one gram negative bacteria (*Escherichia coli)* while antifungal activity was done against three strains *Aspergillus niger*, *Candida albicans, S.cerevicae.* Antibacterial screening revealed that compounds exhibit moderate activity as compared to standard. Antifungal screening revealed that compounds exhibit moderate activity as compared to standard.

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