*Journal of the Korean Chemical Society*
**2011**, *Vol. 55, No. 6*
Printed in the Republic of Korea
http://dx.doi.org/10.5012/jkcs.2011.55.6.960

# Synthesis and Antimicrobial Activity of *N*-[2-(aryl/substituted aryl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide

**Asha B. Thomas*, Rabindra K. Nanda, Lata P. Kothapalli, and Avinash D. Deshpande**

*Department of Pharmaceutical Chemistry, Padm. Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pune, Maharashtra, India. *E-mail: dypharmachem@yahoo.co.in*

(Received June 16, 2011; Accepted August 17, 2011)

**ABSTRACT.** A series of isonicotinyl hydrazones and their 4-thiazolidinones have been synthesized by condensation of isonicotinic acid hydrazide with various aromatic aldehydes to yield Schiff's bases, followed by the cyclocondensation of Schiff's bases with 2-mercaptoacetic acid to yield their 4-thiazolidinones. The synthesized compounds have been characterized by their elemental, analytical and spectral studies. All these compounds were evaluated for their invitro antimicrobial activity against a spectrum of non-resistant and resistant microbial organisms. These studies proved that compounds 5e,i against *B. subtilis*; 5e,f,h against *B. anthracis*; 5g,i against *S. aureus* showed good activity at lower concentrations. Compounds 5d-5i displayed significant activity against resistant strain of *K. pneumonia* with minimum inhibitory potency in the concentration range of 2-16 ug/ml.

**Key words:** Antimicrobial activity, Microwave irradiation, Sonication, 4-thiazolidinones, Resistant bacterial strains

## INTRODUCTION

The treatment of infectious diseases still remains an important and challenging problem. The search of novel antimicrobial agents still continues as the clinical use of the existing antimicrobials has been limited by their relatively high risk of toxicity, development of bacterial resistance and pharmacokinetic problems. Antibacterial resistance to a drug can be counteracted by design of new derivatives of existing drugs. Further, pharmacokinetic properties and cellular permeability of a drug can also be modulated by derivatization. Multi drug resistant organisms are becoming common causes of infections in the acute and long term care units in hospitals. The emergence of these resistant bacteria has created a major concern and there is an urgent need of development of newer antibacterial agents.[1,2]

The literature indicates that the hydrazone group plays an important role for the antimicrobial activity. Furthermore, a number of hydrazide-hydrazone derivatives have been claimed to possess interesting antibacterial–antifungal,[3,4] anticonvulsant,[5] antiinflammatory,[6] antimalarial[7] and antituberculosis activities.[8,9]

The broad and potent activity of 4-thiazolidinones has established it as one of the biologically important scaffold. 4-Thiazolidinone analogues possess wide spectrum of biological activities, such as anti-inflammatory,[10] anticonvulsant,[11] antibacterial,[12,13] antifungal,[14,15] ischemic,[16] FSH receptor agonist,[17] anti-HIV[18] and anticancer[19] activities.

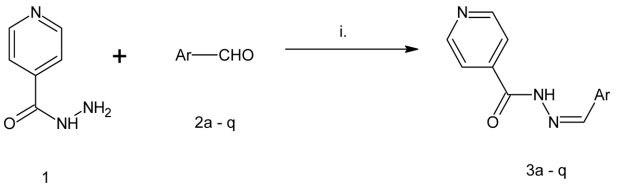
Thiazolidinones have also been reported as inhibitors of bacterial enzyme Mur B, which is an important precursor in the biosynthesis of peptidogylcan of the bacterial cell wall. Several 5-(4-hydroxybenzylidene)-3-(4-methoxybenzyl)-2-(4-methoxybenzylimino)thiazolidin-4-one and their corresponding 5-arylidine derivatives,[20] 2,3-disubstituted-1,3-thiazolidin-4-one derivatives[21] and N-[(2)-3-(4-alkyl/arylsubstituted)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy)-acetohydrazide[22] compounds when evaluated for antibacterial activity against the Gram-positive and Gram-negative strains of bacteria, showed good antibacterial activity. Bondock *et al*. reported some new 4-thiazolidinones synthesized from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde for their antimicrobial activity.[23,24] Several researchers have also investigated the antifungal activity of several derivatives of 4-thiazolidinones.[25]

In the view of above mentioned findings and as continuation of our efforts to identify new candidates that may be of value in designing new potent, selective, and less toxic and less resistant antimicrobial agents, we report herein in the present work the synthesis and antimicrobial screening of some new 4-thiazolidinone derivatives starting from isonicotinic acid hydrazide.

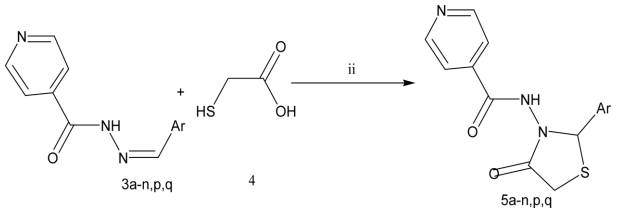
## RESULTS AND DISCUSSION

### Chemistry

The synthetic strategies adopted to obtain the interme-




***Scheme* 1.** Microwave assisted synthesis of intermediate Schiff's bases of INH. Reagents and conditions: i. $H_2O$, MWI, Power level 3(240 W, 35% irradiation).




***Scheme* 2.** Ultrasound assisted synthesis of 4-thiazolidinone analogues using Schiff's bases. Reagents and conditions: ii. Anhydrous $ZnCl_2$, molecular sieves [MS (1-2 gms, 3A×1.5 mm)], THF, sonication.

diate and target compounds are illustrated in *Scheme* 1 and 2. The *N*′-[(*Z*)-(substituted aromatic)methylidene]pyridine-4-carbohydrazide (3a-q) were prepared in excellent yields in a one step reaction (*Scheme* 1) of isonicotinyl hydrazone (INH,1) with various substituted aryl/heteroaryl aldehydes (2a-q) in water using our previously reported microwave irradiation method. The microwave method required shorter reaction times (6-9 mins for completion of reaction) with improved yields (87.5-98.76%) as compared to the reported conventional methods. The reported microwave methods were carried out in the presence of different organic solvents[26-29] as compared to the use of water as a solvent in our reported method. The synthesized Schiff's base intermediates were characterized by the presence of strong band at 1531-1620 $cm^{-1}$ for the N=C imino group. The $^1$H-NMR spectra also showed a signal equivalent to 1 proton for =CH group between 7.4-9.48 ppm, confirming the formation of Schiff's bases. The $^1$H-NMR spectra also exhibited a signal between 7.01-8.66 ppm for the N-H proton. Also, the $^3$J coupling constants of these two protons were almost negligible. However, the theoretical 3D optimisations of the synthesized compounds 3a-q using ChemDraw Ultra 8.0, V-Life Molecular Design Software Version 3.0 and ACD/ChemSketch indicated that the bulky substituted phenyl and pyridine carboxamide groups are at the same side of the N=C bond, indicating the Z-configuration of the Schiff's bases. The Z-configuration will be further confirmed through NOE (Nuclear Overhauser effect) experiments. However, in the $^1$H-NMR spectra of *N*′-[(1Z, 2E)-3-phenylprop-2-en-1-ylidene]pyridine-4-carbohydrazide (3k), the coupling constants of the two olefinic protons (C=C) is 16Hz which states that the two olefinic protons locate on opposite sides of the C=C bond. This indicates that the carbon-carbon double bond in 3k possess E configuration.

The 4-thiazolidinones (5) were synthesized as per our reported method of sonication. The key intermediate Schiff's bases (3a-n,p,q) on reaction with mercaptoacetic acid in presence of anhydrous $ZnCl_2$ and molecular sieves afforded the *N*-[2-(aryl/substituted aryl)-4-oxo-1,3-thiazolidin-3-]pyridine-4-carboxamides derivatives(5a-n,p,q) containing the 4-thiazolidinone nucleus by sonication in very high yield (80.3-96.8%) (*Scheme* 2) in shorter reaction times (30-45 min for the completion of the reaction).

In the $^1$H-NMR spectra of all compounds of series 5, a singlet signal equivalent to 1 proton between 5.22-7.51 ppm (C-2, CH) and a doublet of doublet signal equivalent to 2 protons between 3.35-3.93 ppm; 3.14- 3.85 ppm (C-5, $CH_2$) was observed. This was considered to be a strong confirmation of ring closure representing the formation of thiazolidinone nucleus. In the IR spectra of the same compounds, strong bands at 1708-1743$cm^{-1}$ for the ring carbonyl group (C=O, cyclic) also confirmed the thiazolidinone nucleus formation. The calculated J (coupling constant) values in the range of 8-16 Hz justified the presence of the geminal protons at the C-5 position of the thiazolidinone ring. The elemental analysis results were within ± 0.4% of the theoretical values.

**Antimicrobial activity**

The anti-microbial activity of all compounds (3a-q; 5a-n, p-q) were evaluated by broth dilution method using Mueller-Hinton broth for bacteria and Sabouraud liquid medium for fungi in the concentration range of 0.78-100 ug/ml. The antimicrobial activity of all the screened compounds, determined in terms of the minimum inhibitory concentrations (MIC, μg/mL) are presented in *Table* 1 and 2 respectively. Ampicillin and griseofulvin were used as the standard drugs. The investigated intermediate Schiff's bases displayed very weak inhibition of growth of both bacteria and fungi with MIC in the range of 125-1000 μg/mL. Among the synthesized hydrazones, compounds 3o with a 2,5 dimethoxy substitution on the aryl ring was found to be the most active compound in the series (MIC: 125 μg/ml against *S. aureus*, *E. coli*, *P. chrysogenum* and *A. terrus* respectively). However, all the 4-thiazolidinone derivatives showed improved inhibitory activity than their respective Schiff's bases with MIC ranging from 1.56-200 μg/mL against the tested bacterial

***Table* 1.** Antimicrobial activity of Schiff's bases of INH

| Compounds | Minimum Inhibitory Concentration (MIC[a]) in μg/mL | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Gram positive bacteria | | | Gram negative bacteria | | | Fungi | | |
| | *Bacillus subtilis* | *Staphylococcus aureus* | *Bacillus anthracis* | *Escherichia coli* | *Klebsiella pneumonia* | *Enterobactor aerogenes* | *Aspergillus niger* | *Aspergillus terrus* | *Penicillium chrysogenum* |
| **3a-3i** | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] |
| **3j** | 250 | >250[b] | >250[b] | 250 | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] |
| **3k-3l** | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] |
| **3m** | >250[b] | >250[b] | 250 | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] |
| **3n** | >250 | 250 | 250 | 250 | >250[b] | 250 | >250[b] | 250 | >250 |
| **3o** | 250 | 125 | 250 | 125 | 250 | 250 | 250 | 125 | 125 |
| **3p** | 250[b] | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| **3q** | >250[b] | >250 | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] | >250[b] |
| **Amp[c]** | 3.13 | 3.13 | 3.13 | 3.13 | 3.13 | 3.13 | -- | -- | -- |
| **Gre[d]** | -- | -- | -- | -- | -- | -- | 3.13 | 3.13 | 3.13 |

[a]MIC: Lowest concentration of an antimicrobial agent that significantly inhibits the visible growth of microorganism after a period of incubation.
[b]No inhibition upto a highest concentration of 250 μg/ml.
[c]Amp: Ampicillin.
[d]Gre: Greseofulvin.

***Table* 2.** Antimicrobial activity of synthesized 4-thiazolidinone analogues

| Compounds | Minimum Inhibitory Concentration (MIC[a]) in μg/mL | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Gram positive bacteria | | | Gram negative bacteria | | | Fungi | | |
| | *Bacillus subtilis* | *Staphylococcus aureus* | *Bacillus anthracis* | *Escherichia coli* | *Klebsiella pneumonia* | *Enterobactor aerogenes* | *Aspergillus niger* | *Aspergillus terrus* | *Penicillium chrysogenum* |
| **5a** | 6.25 | 12.5 | 12.5 | 6.25 | 6.25 | 6.25 | 25 | 12.5 | 12.5 |
| **5b** | 50 | 25 | 6.25 | 50 | 12.5 | 12.5 | 12.5 | 25 | 12.5 |
| **5c** | 25 | 12.5 | 6.25 | 6.25 | 12.5 | 6.25 | 3.125 | 6.25 | 25 |
| **5d** | 12.5 | 6.25 | 6.25 | 6.25 | 12.5 | 6.25 | 12.5 | 12.5 | 6.25 |
| **5e** | 3.125 | 6.25 | 3.125 | 6.25 | 6.25 | 12.5 | 12.5 | 6.25 | 25 |
| **5f** | 25 | 12.5 | 3.125 | 6.25 | 6.25 | 6.25 | 6.25 | 6.25 | 12.5 |
| **5g** | 12.5 | 1.56 | 6.25 | 6.25 | 12.5 | 12.5 | 3.125 | 6.25 | 6.25 |
| **5h** | 6.25 | 12.5 | 3.125 | 25 | 6.25 | 12.5 | 12.5 | 12.5 | 12.5 |
| **5i** | 3.125 | 3.125 | 12.5 | 6.25 | 12.5 | 6.25 | 6.25 | 6.25 | 25 |
| **5j** | 50 | 100 | 25 | 200 | 200 | 100 | 200 | 200 | 50 |
| **5k** | 50 | 100 | 100 | 100 | 200 | 100 | 100 | 100 | 50 |
| **5l** | 100 | 25 | 25 | 200 | 200 | 200 | 200 | 50 | 50 |
| **5m** | 12.5 | 6.25 | 6.25 | 12.5 | 12.5 | 12.5 | 12.5 | 25 | 25 |
| **5n** | 50 | 50 | 25 | 100 | 100 | 50 | 100 | 100 | 25 |
| **5p** | 25 | 50 | 50 | 100 | 100 | 100 | 100 | 50 | 50 |
| **5q** | 100 | 200 | 100 | 200 | 200 | 200 | 100 | 100 | 50 |
| **Amp[c]** | 3.13 | 3.13 | 3.13 | 3.13 | 3.13 | 3.13 | -- | -- | -- |
| **Gre[d]** | -- | -- | -- | -- | -- | -- | 3.13 | 3.13 | 3.13 |

[a]MIC: Lowest concentration of an antimicrobial agent that significantly inhibits the visible growth of microorganism after a period of incubation.
[b]No inhibition upto a highest concentration of 250 μg/ml.
[c]Amp: Ampicillin.
[d]Gre: Greseofulvin.

strains and 3.13-200 μg/mL against the tested fungal strains.

From the results obtained it was observed that the compounds bearing electron withdrawing nitro substituent at the para and ortho positions of phenyl groups as in *N*-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5f), and *N*-[2-(2-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5g), was noteworthy and exhibited good inhibitory activity with MIC of 3.13

μg/ml for both compounds against the gram-positive bacterial strain *B. anthracis* as compared to the m-nitro isomer 5g (MIC: 6.25 μg/ml). However the compound 5g was found to possess highest antibacterial potency towards *S.aureus* with MIC value 1.56 μg/ml. The introduction of halogens such as fluorine at the para position and chlorine at the meta position of the phenyl group in *N*-[2-(4-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5i) and *N*-[2-(3-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide(5e) exhibited high activity against *B.subtilis* with MIC of 3.13 μg/ml respectively.

The 4-thiazolidinones were found to be less active against the tested gram-negative bacterial organisms with MIC ranging from 6.25-200 μg/ml. Compound 5f with the electron withdrawing nitro group at the para position of the phenyl ring was the most active with MIC of 6.25 μg/ml against all the tested gram-negative strains. It was also observed that compounds 5c (p-OH isomer) and 5g (m-$NO_2$ isomer) showed comparatively good activity against all the fungal strains (MIC: 3.13 μg/ml against *A.niger*; 6.25 μg/ml against *A.terrus*). Results confirmed that the effectiveness of the 4-thiazolidinone derivatives was governed in part by the substituents present on the phenyl ring. The presence of electron withdrawing substituents like chloro and nitro group on the aryl ring was found to contribute significantly to the antibacterial activity against the gram positive bacterial strains. Some of the synthesized 4-thiazolidinones were found to be more active as compared to the standard drugs, Ampicillin and Griseofulvin against the tested microbial strains.

The most potent compounds 5d-5i were further evaluated against drug resistant bacterial strains *E.coli, S. aureus* and *K. pneumonia* obtained from clinical isolates (*Table* 3). All the screened compounds showed minimum to moderate inhibition potency against resistant strains of *E.coli* and *S.aureus* with MIC ranging from 125-200 μg/ml. However, all the tested compounds exhibited significant inhibitory potency with MIC in the range of 2-16 μg/ml against *K. pneumonia.*

***Table* 3. Antimicrobial activity of synthesized 4-thiazolidinone analogues (5d-i) against resistant bacterial strains**

| Compounds | Minimum Inhibitory Concentration (MIC[a]) in μg/mL | | |
|---|---|---|---|
| | *Staphylococcus aureus** | *Escherichia coli** | *Klebsiella pneumonia** |
| **5d** | 250 | 250 | 2 |
| **5e** | 250 | 250 | 4 |
| **5f** | 250 | 500 | 8 |
| **5g** | 125 | 125 | 4 |
| **5h** | 125 | 125 | 4 |
| **5i** | 250 | 500 | 16 |

[a]MIC: Lowest concentration of an antimicrobial agent that significantly inhibits the visible growth of microorganism after a period of incubation

*Resistant strains obtained from clinical isolates.

## Conclusions

A new series of 4-thiazolidinones have been synthesized from isonicotinic acid hydrazide employing green route method of microwave irradiation and sonication with good to excellent yields. The compounds showed promising antimicrobial activity in vitro against both, the non-resistant and resistant microbial strains and can be further modified to exhibit better potency than the standard drugs. The structural and electronic diversity of these compounds influenced their activity. It can be concluded that this class of compounds certainly holds great promise towards the pursuit to discover novel class of antimicrobial agents. Further studies to acquire more information about quantitative structure-activity relationships and mechanistic mode of action are underway.

## EXPERIMENTAL SECTION

Melting points (mp) were determined on a Veego melting point apparatus (VMP PM, 32/1104) and are uncorrected. Thin layer chromatography was carried out using readymade silica gel plates (Merck). UV studies were carried out on UV Visible spectrophotometer (Shimadzu 1700). IR spectra (KBr) were recorded on a FTIR spectrophotometer with Diffuse Reflectance attachment (Shimadzu 8400S). $^1$H-NMR spectra were obtained on NMR Spectrophotometer (Bruker Avance II 400 NMR) using dimethyl sulphoxide-$d_6$ as the solvent. Chemical shifts were expressed in parts per million relative to $SiMe_4$ as internal standard. The mass spectra were obtained on a Hewlett Packard Electron Impact mass spectrometer GCD-1800A (70 eV EI source) using direct insertion probe and Quadrapole TOF Mass spectrometer using electrospray ionisation (Positive mode). Microanalyses were performed on a Thermo Finnigan C, H, N analyzer. Chemicals were obtained from Qualigens, Acros and Aldrich chemicals Co. and used without further purification. All other solvents, unless otherwise specified were of analytical reagent grade or of the highest quality commercially available.

### Chemistry

**Synthesis of *N'*-[(*Z*)-(aryl/substituted aryl)methylidene] pyridine-4-carbohydrazides (3a-q)**

The synthesis of compounds (3a-q) was performed

according to our previously reported procedure (*Scheme* 1).[30] The crude product upon recrystallisation from alcohol gave the pure hydrazones of INH (3a-q). The synthesized compounds were characterized by their M.P. and spectral data (UV, IR, $^1$H NMR, MS, CHN).

***N'*-[(*Z*)-phenylmethylidene]pyridine-4-carbohydrazide (3a):** White crystals, yield 86.7, mp 194-196 °C, IR ($\nu_{max}$, cm$^{-1}$, KBr): 3197 (NH), 3028 (CH), 1693 (amide-I, C=O), 1600 (imine C=N); $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 9.44-9.53 (d, 2H, pyridine), 8.78-8.81 (d, 2H, pyridine), 8.37 (s, 1H, NH), 7.57-7.89 (s, 5H, aromatic), 7.43 (s, 1H, CH). MS: m/z 226.5 $(M + H)^+$. Anal. Calcd for $C_{13}H_{11}N_3O_2$ (241.25): C, 64.72; H, 4.60; N, 17.42%, Found: C, 64.51; H, 4.73; N, 17.60%.

***N'*-[(*Z*)-(2-hydroxyphenyl)methylidene]pyridine-4-carbohydrazide (3b):** White crystals, yield 95.6, mp 262-264 °C, IR ($\nu_{max}$, cm$^{-1}$, KBr): 3344 (-OH), 3178 (-NH), 3004 (-CH), 1685 (amide-I, C=O), 1566 (imine C=N). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 11.0 (s, OH), 8.8-8.9 (d, Pyridine 2H), 8.6-8.8 (d, Pyridine 2H), 8.7 (s, CH), 7.5-7.6 (d, Aromatic1H), 8.6 (s, NH), 6.8-7.0 (d, Aromatic 2H), 7.3-7.4 (m, Aromatic 1H). MS: m/z 242.5$(M + H)^+$. Anal. Calcd for $C_{13}H_{11}N_3O_2$ (241.25): C, 64.72; H, 4.60; N, 17.42%, Found: C, 64.51; H, 4.73; N, 17.60%.

***N'*-[(*Z*)-(4-hydroxyphenyl)methylidene]pyridine-4-carbohydrazide (3c):** Yellow powder, yield 94.5, mp 264-268 °C, IR ($\nu_{max}$, cm$^{-1}$, KBr): 3340 (-OH), 3213 (-NH), 3055 (-CH), 1662 (amide-I, C=O), 1608 (imine C=N). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 11.5 (s, OH), 8.8-8.5 (d, Pyridine 2H), 8.4-8.3 (d, Pyridine 2H), 7.8 (s, CH), 8.0 (s, NH) 7.5-7.3 (d, Aromatic 2H), 7.0-6.8 (d, Aromatic 2H). MS: m/z 242.5$(M+H)^+$. Anal. Calcd for $C_{13}H_{11}N_3O_2$ (241.25): C, 64.72; H, 4.60; N, 17.42%, Found: C, 64.57; H, 4.52; N, 17.36%.

***N'*-[(*Z*)-(4-chlorophenyl)methylidene]pyridine-4-carbohydrazide (3d):** White crystals, yield 98.1, mp 218-221 °C, IR ($\nu_{max}$, cm$^{-1}$, KBr): 3166 (-NH), 3020 (-CH), 1674 (amide-I, C=O), 1593 (imine C=N), 698 (-Cl). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.88-8.91 (d, Pyridine 2H), 8.32 (s, CH), 8.65 (s, NH), 7.99-8.05 (d, Pyridine 2H), 7.79-7.80 (d, Aromatic 2H), 7.50-7.51 (d, Aromatic 2H). MS: m/z 260.4$(M+H)^+$. Anal. Calcd for $C_{13}H_{10}ClN_3O$ (259.69): C, 60.12; H, 3.88; N, 16.18%, Found: C, 60.34; H, 3.76; N, 16.13%.

***N'*-[(*Z*)-(3-chlorophenyl)methylidene]pyridine-4-carbohydrazide (3e):** White powder, yield 87.5, mp 253-258 °C, IR ($\nu_{max}$, cm$^{-1}$, KBr): 3190 (-NH), 3021 (-CH), 1681 (amide-I, C=O), 1600 (imine C=N) 686 (-Cl). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.70-8.90 (d, Pyridine 2H ), 8.44 (s, CH), 8.02 (s, NH), 7.71-7.72 (d, Pyridine 2H), 7.47 (s, Aromatic 1H), 7.35-7.37 (d, Aromatic 2H), 7.30-7.42 (m, Aromatic 2H). MS: m/z 260.4 $(M+H)^+$. Anal. Calcd for $C_{13}H_{10}ClN_3O$ (259.69): C, 60.12; H, 3.88; N, 16.18%, Found: C, 60.22; H, 3.7 8; N, 16.10%.

***N'*-[(*Z*)-(4-nitrophenyl)methylidene]pyridine-4-carbohydrazide (3f):** Yellow powder, yield 90.7, mp 255-257 °C, IR ($\nu_{max}$, cm$^{-1}$, KBr): 3186 (-NH), 3001 (-CH), 1685 (amide-I, C=O), 1558 (imine C=N), 1334, 1512 (-$NO_2$). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 9.32-9.35 (d, Pyridine 2H), 8.51-8.55 (d, Pyridine 2H), 8.34 (s, NH), 8.10 (s, CH), 7.89-7.93 (d, Aromatic 2H), 7.60-7.62 (d, Aromatic 2H). MS: m/z 271.4 $(M+H)^+$. Anal. Calcd for $C_{13}H_{10}N_4O_3$ (270.24): C, 57.78; H, 3.73; N, 20.73%, Found: C, 58.07; H, 3.68; N, 20.51%.

***N'*-[(*Z*)-(3-nitrophenyl)methylidene]pyridine-4-carbohydrazide (3g):** Yellow powder, yield 87.8, mp 195-198 °C, IR ($\nu_{max}$,cm$^{-1}$,KBr): 3218(-NH), 3083(-CH), 1695 (amide-I, C=O), 1612(imine C=N), 1353, 1531 (-$NO_2$).$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 9.03-8.78 (d, Pyridine 2H), 7.81-7.88 (d, Pyridine 2H), 8.34 (s, NH), 8.60 (s, Aromatic 1H), 8.58 (s, CH), 8.13-8.15 (d, Aromatic 1H), 8.03-8.05 (d, Aromatic 1H), 7.60-7.74 (m, Aromatic 1H). MS: m/z 271.4$(M+H)^+$. Anal. Calcd for $C_{13}H_{10}N_4O_3$ (270.24): C, 57.78; H, 3.73; N, 20.73%, Found: C, 58.11; H, 3.63; N, 20.61%.

***N'*-[(Z)-(2-Nitrophenyl)methylidene] pyridine-4-carbohydrazide (3h):** Yellow powder, yield 99.2, mp 229-231 °C, IR ($\nu_{max}$, cm$^{-1}$, KBr): 3193 (-NH), 3018 (-CH), 1677 (amide-I, C=O), 1552 (imine C=N), 1517, 1363 (-NO2). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 9.04 (s CH), 8.77-8.78 (d, Pyridine 2H), 8.62 (s, NH), 8.27-8.29 (d, Aromatic 1H), 8.04-8.06 (d, Aromatic 1H), 7.88-7.89 (d, Pyridine 2H), 7.70-7.74 (m, Aromatic 1H), 7.59-7.63 (m, Aromatic 1H). MS: m/z 271.5 $(M+H)^+$. Anal. Calcd for $C_{13}H_{10}N_4O_3$ (270.24): C, 57.78; H, 3.73; N, 20.73%. Found: C, 57.92; H, 3.66; N, 20.95%.

***N'*-[(Z)-(4-Flurophenyl)methylidene]pyridine-4-carbohydrazide (3i):** White powder, yield 98.7, mp 189-190 °C, IR ($\nu_{max}$, cm$^{-1}$, KBr): 3172 (-NH), 3064 (-CH), 1660 (amide-I, C=O), 1568 (imine C=N), 1301 (C-F). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.75-8.76 (d, Pyridine 2H), 8.46 (s,CH), 8.05 (s,-NH), 7.83-7.84 (d, Pyridine 2H), 7.77-7.80 (d, Aromatic 2H), 7.08-7.10 (d, Aromatic 2H). MS: m/z 244.4 $(M+H)^+$. Anal. Calcd for $C_{13}H_{10}FN_3O$ (243.24): C, 64.19; H, 4.14; N, 17.28%. Found: C, 64.83; H, 4.52; N, 18.02%.

***N*'-[(Z)-(4-Methoxyphenyl)methylidene]pyridine-4-carbohydrazide (3j):** Off white powder, yield 90.98, mp 170-173 °C. IR ($\nu_{max}$, $cm^{-1}$, KBr): 3157 (-N-H), 3037 (-CH), 2995 (-CH), 1665 (amide-I, C=O), 1598 (C=N), 1477 (-$CH_3$). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.75-8.85 (d, Pyridine 2H), 8.35 (s, -CH), 7.63-7.70 (d, Pyridine 2H, d, Aromatic 2H), 7.4 (s, -NH), 6.84-6.89 (d, Aromatic 2H), 3.78 (s, -$OCH_3$ 3H). MS: m/z 256.5 $(M+H)^+$. Anal. Calcd for $C_{14}H_{13}N_3O_2$ (255.27): C, 65.87; H, 5.13; N, 16.46%. Found: C, 65.43; H, 5.64; N, 16.80%.

**N'-[(1Z,2E)-3-phenylprop-2-en-1-ylidene]pyridine-4-carbohydrazide (3k):** Orange powder, yield 95.6, mp 204-206 °C. IR ($\nu_{max}$, $cm^{-1}$, KBr): 3234 (-N-H), 3056 (-CH), 2934 (-CH), 1676(amide-I, C=O), 1542(C=N), 1406 (alkene -CH). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.55-8.80 (d, Pyridine 2H), 8.16 (s, -CH), 7.70-7.80 (d, Pyridine 2H), 7.28-7.40 (m, Aromatic 5H), 7.01 (s, -NH), 6.92-6.97 (m, Alkene HC=CH 2H). MS: m/z 252.4 $(M+H)^+$. Anal. Calcd for $C_{15}H_{13}N_3O$ (251.28): C, 71.70; H, 5.21; N, 16.72%. Found: C, 71.91; H, 5.19; N, 16.82%.

***N*'-[(Z)-(4-Hydroxy-3-methoxyphenyl)methylidene]-pyridine-4-carbohydrazide (3l):** Yellow powder, yield 94.18, mp 226-228 °C. IR ($\nu_{max}$, $cm^{-1}$, KBr): 3517 (O-H), 3218 (-N-H), 3064 (-CH), 2985 (Alkane -CH), 1664 (amide-I, C=O), 1596 (C=N), 1568 (-N-H), 1068 (=C-O-C), 810, 881 (1,3,4-tri substituted alkene -CH). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 9.48 (s, -CH), 9.37 (s, -OH), 8.74-8.75 (d, Pyridine 2H), 8.36 (s, -NH), 7.82-7.83 (d, Pyridine 2H), 7.37-7.38 (d, Aromatic 1H), 7.07-7.09 (d, Aromatic 1H), 6.64-6.68 (d, Aromatic 1H), 3.87 (s, -$CH_3$). MS: m/z 272.4 $(M+H)^+$. Anal. Calcd for $C_{14}H_{13}N_3O_3$ (271.27): C, 61.99; H, 4.83; N, 15.49%. Found: C, 62.17; H, 4.92; N, 16.04%.

**(Z)-*N*'-((Furan-2-yl)methylene)isonicotinohydrazide (3m):** Brownish powder, yield 92.09, mp 208-212 °C. IR ($\nu_{max}$, $cm^{-1}$, KBr): 3271(-NH), 3051 (-CH), 1650 (amide-I, C=O), 1620 (imine C=N), 1350 (C-O). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.91-8.89 (d, Pyridine 2H), 8.32 (s, CH), 8.18-8.13 (d, Pyridine 2H), 7.84 (s, -NH), 7.54-7.52 (d, Furan 1H), 6.85-6.55 (m, Furan 2H), 5.97-5.92 (d, Furan 1H). MS: m/z 216.4 $(M+H)^+$. Anal. Calcd for $C_{11}H_9N_3O_2$ (215.21): C, 61.39; H, 4.22; N, 19.53%. Found: C, 61.27; H, 4.13; N, 19.64%.

***N*'-{(Z)-[4-(Dimethylamino)phenyl]methylidene}-pyridine-4-carbohydrazide (3n):** Yellow powder, yield 97.16, mp 104-106 °C. IR ($\nu_{max}$, $cm^{-1}$, KBr): 3153 (-N-H), 3045 (-CH), 2961 (-CH), 1664 (amide-I, C=O), 1604 (imine C=N). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.73-8.72 (d, Pyridine 2H), 8.35 (s, CH), 8.07 (s, -NH), 7.82-7.84 (d, Pyridine 2H), 7.62-7.60 (d, Aromatic 2H), 6.69-6.66 (d, Aromatic 2H), 3.07 (s, -$CH_3$ 6H). MS: m/z 269.5 $(M+H)^+$. Anal. Calcd for $C_{15}H_{16}N_4O$ (268.31): C, 67.15; H, 6.01; N, 20.88%. Found: C, 67.58; H, 6.12; N, 21.13%.

***N*'-[(Z)-(2,5-Dimethoxyphenyl)methylidene]pyridine-4-carbohydrazide (3o):** Brown crystals, yield 95.2, mp 185-188 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3190 (-NH), 3061 (-CH), 1654 (amide-I, C=O), 1550 (imine C=N), 1060 (O-$CH_3$). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.89-8.92 (d, Pyridine 2H), 8.22 (s, CH), 8.48 (s, NH), 8.11-8.15 (d, Pyridine 2H), 7.5-7.8 (d of d, Aromatic 2H), 6.92 (s, Aromatic 1H), 3.92-4.12 (m, O-CH3). MS: m/z 286.5 $(M+H)^+$. Anal. Calcd for $C_{15}H_{15}N_3O_3$ (285.3): C, 63.15; H, 5.30; N, 14.73%. Found: C, 63.49; H, 5.21; N, 14.84%.

***N*'-[(*Z*)-(5-nitrothiophen-2-yl)methylidene]pyridine-4-carbohydrazide (3p):** Brown powder, yield 90.3, mp 173-175 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3390 (-NH), 3031 (-CH), 1674 (amide-I, C=O), 1531 (imine C=N), 1500, 1338 (-NO2). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.76-8.79 (d, Pyridine 2H), 8.22 (s, CH), 8.06-8.07 (d, Pyridine 2H), 7.88-7.89 (d, Thiophene 1H), 7.36-7.37 (d, Thiophene 1H), 7.26 (s, NH). MS: m/z 277.5 $(M+H)^+$. Anal. Calcd for $C_{11}H_8N_4O_3S$ (276.27): C, 47.82; H, 2.92; N, 20.28%. Found: C, 48.09; H, 2.84; N, 20.24%.

***N*'-[(*Z*)-(2-hydroxynaphthalen-1-l)methylidene]pyridine-4-carbohydrazide (3q):** Pale yellow powder, yield 89.1, mp 257-260 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3240 (-OH), 3070 (-NH), 3020 (-CH), 1639 (amide-I, C=O), 1593 (imine C=N), 1500. $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.80-8.81 (d, Pyridine 2H), 8.15-8.17 (d, Pyridine 2H), 8.04-6.87 (m, Aromatic 6H), 7.74 (s, CH), 8.26 (s, NH). MS: m/z 292.5 $(M+H)^+$. Anal. Calcd for $C_{17}H_{13}N_3O_2$ (291.30): C, 70.09; H, 4.50; N, 14.42%. Found: C, 70.17; H, 4.54; N, 14.34%.

**Synthesis of *N*-[2-(aryl/substituted aryl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamides (5a-n,p,q)**

The 4-thiazolidinones (5a-n,p,q) were synthesized as per our reported green route method of sonication (*Scheme* 2).[31] The crude product on recrystallisation from alcohol yielded the pure 4-thiazolidinones of isonicotinoyl hydrazones (5a-n,p,q). The synthesized compounds were characterized by their M.P., TLC ($R_f$ values) and spectral data (UV, IR, 1H NMR, MS, CNH).

***N*-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)pyridine-4-carboxamide (5a):** White powder, yield 92.0, mp 250-253 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3256 (NH), 3028 (CH), 1743 (ring C=O), 1650 (amide C=O). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.68-8.77(d, 2H, pyridine), 8.75 (s, 1H, NH),

7.73-7.75 (d, 2H, pyridine), 7.69-7.71 (s, 5H, aromatic), 5.96 (s, 1H, CH), 3.35- 3.40 (d, 1H, $CH_2$), 3.24-3.29 (d, 1H, $CH_2$). MS: m/z 299 $(M)^+$. Anal. Calcd for $C_{15}H_{13}N_3O_2S$ (299.35): C, 60.18; H, 4.38; N, 14.04%, Found: C, 59.82; H, 4.42; N, 14.52%.

***N*-[2-(2-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5b):** White powder, yield 89.7, mp 268-271 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3344 (OH), 3217 (NH), 3039 (CH), 1739 (ring C=O), 1697 (amide C=O). $^1H$ NMR (400 MHz, DMSO-$d_6$): δ ppm 8.95-8.97 (d, 2H, pyridine), 8.11-8.12 (d, 2H, pyridine), 7.45 (s, 1H, NH), 6.87-7.47 (m, 4H, aromatic), 6.22 (s, 1H, OH), 5.69 (s, 1H, CH), 3.47- 3.48 (d, 1H, $CH_2$), 3.26-3.29 (d, 1H, $CH_2$). MS: m/z 315$(M)^+$. Anal. Calcd for $C_{15}H_{13}N_3O_3S$ (315.35): C, 57.13; H, 4.16; N, 13.33%, Found: C, 57.27; H, 4.12; N, 13.19%.

***N*-[2-(4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5c):** Yellow powder, yield 90.2, mp >290 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3445 (OH), 3217 (NH), 3052 (CH), 1724 (ring C=O), 1668 (amide C=O). $^1H$ NMR (400 MHz, DMSO-$d_6$): δ ppm 8.75-8.77 (d, 2H, pyridine), 8.06 (s, 1H, NH), 7.84-7.85 (d, 2H, pyridine), 7.73-7.75 (d, 2H, aromatic), 7.29-7.34 (d, 2H, aromatic), 6.05 (s, 1H, CH), 5.36 (s, 1H, OH), 3.66- 3.70 (d, 1H, $CH_2$), 3.54-3.59 (d, 1H, $CH_2$). MS: m/z 315$(M)^+$. Anal. Calcd for $C_{15}H_{13}N_3O_3S$ (315.35): C, 57.13; H, 4.16; N, 13.33%, Found: C, 57.38; H, 3.92; N, 13.66%.

***N*-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5d):** White crystals, yield 96.8, mp 239-242 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3159 (NH), 3082 (CH), 1728 (ring C=O), 1674 (amide C=O), 1083 (C-Cl). $^1H$ NMR (400 MHz, DMSO-$d_6$): δ ppm 8.75-8.77 (d, 2H, pyridine), 8.07 (s, 1H, NH), 7.84-7.85 (d, 2H, pyridine), 7.73-7.75 (d, 2H, aromatic), 7.69-7.71 (d, 2H, aromatic), 6.05 (s, 1H, CH), 3.73-3.77 (d, 1H, $CH_2$), 3.60-3.64 (d, 1H, $CH_2$). MS: m/z 333$(M)^+$. Anal. Calcd for $C_{15}H_{12}ClN_3O_2S$ (333.79): C, 53.97; H, 3.62; N, 12.59%, Found: C, 55.02; H, 3.89; N, 12.02%.

***N*-[2-(3-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5e):** White crystals, yield 89.2, mp 215-218 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3070 (NH), 3024 (CH), 1708 (ring C=O), 1693 (amide C=O), 1076 (C-Cl). $^1H$ NMR (400 MHz, DMSO-$d_6$): δ ppm 8.91-8.92 (d, 2H, pyridine), 8.33 (s, 1H, NH), 8.14-8.16 (d, 2H, pyridine), 7.60 (s, 1H, aromatic), 7.56-7.88 (m, 3H, aromatic), 5.48 (s, 1H, CH), 3.42-3.46 (d, 1H, $CH_2$), 3.18-3.22 (d, 1H, $CH_2$). MS: m/z 333$(M)^+$. Anal. Calcd for $C_{15}H_{12}ClN_3O_2S$ (333.79): C, 53.97; H, 3.62; N, 12.59%, Found: C, 54.31; H, 3.55; N, 12.42%.

***N*-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5f):** Yellow powder, yield 86.4, mp 263-266 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3120 (NH), 3060 (CH), 1720 (ring C=O), 1681 (amide C=O), 1519,1338 (-$NO_2$). $^1H$ NMR (400 MHz, DMSO-$d_6$): δ ppm 9.07-9.02 (d, 2H, pyridine), 8.73 (s, 1H, NH), 8.13-8.11 (d, 2H, pyridine), 7.95-7.93 (d, 2H, aromatic), 7.71-7.70 (d, 2H, aromatic), 5.91 (s, 1H, CH), 3.40- 3.35 (d, 1H, $CH_2$), 3.31-3.26 (d, 1H, $CH_2$). MS: m/z 344$(M)^+$. Anal. Calcd for $C_{15}H_{12}N_4O_4S$ (344.35): C, 52.32; H, 3.51; N, 16.27%, Found: C, 52.58; H,3.68; N, 17.06%.

***N*-[2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5g):** Yellow powder, yield 82.4, mp 249-252 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3159 (-NH), 3082 (-CH), 1728 (ring C=O), 1674 (amide I, -C=O), 1523,1350 (-$NO_2$). $^1H$ NMR (400 MHz, DMSO-$d_6$): δ ppm 8.90-8.92 (d, 2H, pyridine), 8.33 (s, 1H, NH), 8.14-8.16 (d, 2H, pyridine), 7.86-7.88 (m, 2H, aromatic), 7.56-7.60 (m, 2H, aromatic), 5.48 (s, 1H, CH), 3.42- 3.46 (d, 1H, $CH_2$), 3.18-3.22 (d, 1H, $CH_2$). MS: m/z 345.6$(M+1)^+$. Anal. Calcd for $C_{15}H_{12}N_4O_4S$ (344.35): C, 52.32; H, 3.51; N, 16.27%, Found: C, 52.44; H, 3.59; N, 16.16%.

***N*-[2-(2-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5h):** Yellow powder, yield 82.9, mp 255-258 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3180 (-NH), 3066 (-CH), 1712 (ring C=O), 1666 (amide I, -C=O), 1523, 1350 (-$NO_2$). $^1H$ NMR (400 MHz, DMSO-$d_6$): δ ppm 8.81-9.02 (d, 2H, pyridine), 8.73 (s, 1H, NH), 8.25-8.27 (d, 1H, aromatic), 8.05-8.07 (d, 2H, pyridine), 7.57-7.96 (m, 3H, aromatic), 6.38 (s, 1H, CH), 3.75- 3.79 (d, 1H, $CH_2$), 3.22-3.26 (d, 1H, $CH_2$). MS: m/z 345.5$(M+1)^+$. Anal. Calcd for $C_{15}H_{12}N_4O_4S$ (344.35): C, 52.32; H, 3.51; N, 16.27%, Found: C, 52.60; H, 3.69; N, 16.33%.

***N*-[2-(4-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5i):** Yellow powder, yield 94.2, mp 240-242 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3147 (-NH), 3082 (-CH), 1731 (ring C=O), 1666 (amide I, -C=O), 1222(-C-F). $^1H$ NMR (400 MHz, DMSO-$d_6$): δ ppm 8.88-8.89 (d, 2H, pyridine), 7.98-8.03 (d, 2H, pyridine), 7.66 (s, 1H, NH), 7.44-7.45 (d, 2H, aromatic), 7.05-7.06 (d, 2H, aromatic), 5.33 (s, 1H, CH), 3.37- 3.41 (d, 1H, $CH_2$), 3.14-3.18 (d, 1H, $CH_2$). MS: m/z 318.5$(M+1)^+$. Anal. Calcd for $C_{15}H_{12}FN_3O_2S$ (317.34): C, 56.77; H, 3.81; N, 13.24%, Found: C, 56.82; H, 3.87; N, 13.16%.

***N*-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5j):** Brown powder, yield 90.3, mp 278-281 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3267 (-NH), 3040 (-CH), 1710 (ring C=O), 1658 (amide I, -C=O), 1448 (-$CH_3$). $^1H$ NMR (400 MHz, DMSO-$d_6$): δ ppm 8.74-8.75 (d, 2H,

pyridine), 8.42 (s, 1H, NH), 7.83-7.85 (d, 2H, pyridine), 7.72-7.74 (d, 2H, aromatic), 6.93-6.95 (d, 2H, aromatic), 5.89 (s, 1H, CH), 3.82- 3.86 (d, 1H, $CH_2$), 3.75-3.76 (d, 1H, $CH_2$), 3.59 (s, 3H, -$OCH_3$). MS: m/z 330.6$(M+1)^+$. Anal. Calcd for $C_{16}H_{15}N_3O_3S$ (329.37): C, 58.34; H, 4.59; N, 12.76%, Found: C, 58.58; H,4.63; N, 12.80%.

***N*-{4-oxo-2-[(*E*)-2-phenylethenyl]-1,3-thiazolidin-3-yl}pyridine-4-carboxamide (5k):** Yellow powder, yield 87.2, mp 247-250 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3330 (-NH), 3010 (-CH), 1718 (ring C=O), 1660 (amide I, -C=O), 1392 (-CH). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.75-8.76 (d, 2H, pyridine), 8.27 (s, 1H, NH), 7.84-7.85 (d, 2H, pyridine), 7.30-7.52 (m, 5H, aromatic), 6.98-7.02 (d, 2H, alkene), 5.43 (s, 1H, CH), 3.69- 3.71 (d, 1H, $CH_2$), 3.65-3.68 (d, 1H, $CH_2$). MS: m/z 342.6 $(M+1)^+$. Anal. Calcd for $C_{18}H_{19}N_3O_3S$ (341.43): C, 63.32; H, 5.61; N, 12.31%, Found: C, 63.49; H,5.65; N, 12.33%.

***N*-[2-(4-hydroxy-3-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5l):** Pale Yellow powder, yield 80.3, mp 217-219 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3400 (-OH), 3149(-NH), 3008 (-CH), 1710 (ring C=O), 1658 (amide I, -C=O), 1392(-OH). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.74-8.75 (d, 2H, pyridine), 8.38 (s, 1H, NH), 7.84-7.85 (d, 2H, pyridine), 7.42 (s, 1H, OH), 6.86-7.08 (m, 3H, aromatic), 5.85 (s, 1H, CH), 3.91 (s, 3H, -$OCH_3$), 3.66-3.68 (d, 1H, $CH_2$), 3.54-3.56 (d, 1H, $CH_2$). MS: m/z 346.5 $(M+1)^+$. Anal. Calcd for $C_{16}H_{15}N_3O_4S$ (345.37): C, 55.64; H, 4.38; N, 12.17%, Found: C, 55.68; H, 4.47; N, 12.20%.

***N*-(2-furan-2-yl-4-oxo-1,3-thiazolidin-3-yl)pyridine-4-carboxamide (5m):** Brown powder, yield 81.0, mp 198-201 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3271(-NH), 3112 (furan-CH), 1714 (ring C=O), 1664 (amide I, -C=O), 1542, 1404 (Furan ring C=C). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 9.71-9.70 (d, 2H, pyridine), 8.11 (s, 1H, NH), 7.80-7.83 (d, 2H, pyridine), 6.41-7.45 (m, 3H, furfural ring), 5.99 (s, 1H, CH), 3.90- 3.94 (d, 1H, $CH_2$), 3.62-3.66 (d, 1H, $CH_2$). MS: m/z 290.4 $(M+1)^+$. Anal. Calcd for $C_{13}H_{11}N_3O_3S$ (289.31): C, 53.97; H, 3.83; N, 14.52%, Found: C, 54.12; H, 3.88; N, 14.61%.

**N-{2-[4-(dimethylamino)phenyl]-4-oxo-1,3-thiazolidin-3-yl}pyridine-4-carboxamide (5n):** Brown powder, yield 81.6, mp 224-226 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3434 (-NH), 3190 (-CH), 1720 (ring C=O), 1664 (amide I, -C=O), 1367 (-CH). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.75-8.76 (d, 2H, pyridine), 8.34 (s, 1H, NH), 7.85-7.86 (d, 2H, pyridine), 7.69-7.71 (d, 2H, aromatic), 6.68-6.71 (d, 2H, aromatic), 5.22 (s, 1H, CH), 3.91- 3.93 (d, 1H, $CH_2$), 3.84-3.85 (d, 1H, $CH_2$). MS: m/z 343.6 $(M)^+$. Anal. Calcd for $C_{17}H_{18}N_4O_2S$ (342.42): C, 59.63; H, 5.30; N, 16.36%, Found: C, 60.03; H, 5.41; N, 16.42%.

***N*-[2-(5-nitrothiophen-2-yl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5p):** Blackish brown powder, yield 94.3, mp 174-176 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3120 (-NH), 3040 (-CH), 1712 (ring C=O), 1672 (amide I, -C=O), 1502, 1369 (-$NO_2$).$^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 8.77-8.78 (d, 2H, pyridine), 7.97 (s, 1H, NH), 7.85-7.86 (d, 2H, pyridine), 7.43-7.44 (d, 2H, Thiophene), 5.69 (s, 1H, CH), 3.53-3.54 (d, 1H, $CH_2$), 3.45-3.46 (d, 1H, $CH_2$). MS: m/z 351.5 $(M+1)^+$. Anal. Calcd for $C_{13}H_{10}N_4O_4S_2$ (350.37): C, 44.56; H, 2.88; N, 15.99%, Found: C, 44.70; H, 2.95; N, 16.04%.

***N*-[2-(3-hydroxynaphthalen-2-yl)-4-oxo-1,3-thiazolidin-3-yl]pyridine-4-carboxamide (5q):** Brown powder, yield 93.9, mp 258-260 °C, IR ($\nu_{max}$, $cm^{-1}$, KBr): 3480 (-OH), 3047 (-NH), 3010 (-CH), 1708 (ring C=O), 1665 (amide I, -C=O), 1436 (-OH). $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 10.85 (s, 1H, OH), 8.67-8.69 (d, 2H, pyridine), 7.96 (s, 1H, NH), 8.03-8.05 (d, 2H, pyridine), 7.82-7.84 (m, 2H, aromatic), 7.61-7.63 (m, 1H, aromatic), 7.59-7.63 (m, 1H, aromatic), 7.40-7.44 (d, 1H, aromatic), 5.95 (s, 1H, CH), 3.53- 3.54 (d, 1H, $CH_2$), 3.47-3.48 (d, 1H, $CH_2$). MS: m/z 366.6$(M+1)^+$. Anal. Calcd for $C_{19}H_{15}N_3O_3S$ (365.41): C, 62.45; H, 4.14; N, 11.50%, Found: C, 62.58; H, 4.18; N, 11.60%.

### Antimicrobial activity

The antimicrobial susceptibility testing of the synthesized compounds (3a-q;5a-n,p-q) were assayed in vitro by the two-fold broth dilution technique.[32] The microbial strains selected for the study include *B. subtilis* (ATCC 9372, NCIM 2951), *B. anthracis* (ATCC 14579, NCIM B9373), *S. aureus* (ATCC 6538P, NCIM 2079), *E. coli* (ATCC 9637, NCIM2563), *E.aerogenus* (NCIM 5139), *P. aeroginosa* (ATCC 19429, NCIM 2036), *A. niger* (ATCC 10864, NCIM 616), *P. chrysogenum* (ATCC 10002, NCIM 738) *and A. terrus* ATCC10020, NCIM657) procured from the National Collection of Industrial Microorganisms (NCIM), Pune, India. Test drug solutions were dissolved in dimethylsulfoxide and then diluted in culture medium (Mueller-Hinton Broth for bacteria and Sabouraud Liquid Medium for fungi) to obtain final concentrations in the range of 0.78-1000 μg/mL and then assayed to determine the minimal inhibitory concentration (MIC, μg/mL). The amount of inocula was $5\times10^4$ bacteria/mL and $1\times10^3$ fungi/mL. The MIC's were read after incubation at 37±0.5° for antibacterial activity for 24 h and 48 h at 28±0.5° for antifungal activity. Ampicillin and griseofulvin were employed

as reference antibacterial and antifungal agents, respectively.

The most potent compounds were further evaluated for their activity against resistant strains of *E.coli, S.aureus* and *K. pneumonia* obtained from clinical isolates.

**Acknowledgements.** This work was financially supported by University of Pune, Pune (India). The authors thank Padm. Dr. D. Y. Patil Institute of Pharmaceutical Science and Research, Pune (India) for providing the necessary infrastructural facilities to carry out this work. The spectral analysis was carried out by SAIF/CIL, Punjab University, Chandigarh (India). The authors would like to thank Dr. Kishore Bhat, Professor and Head, Microbiology, Maratha Mandal's NGH institute of Dental sciences, Karnataka, India for helping with the antibacterial screening against resistant microorganisms.

## REFERENCES

1. Tomasz, A.; Eng. N. *J. Med*. **1994**, *330*, 1247.
2. Witte, W.; Cuny, C.; Klare, I.; Nubel, U.; Strommenger, B.; Werner, G. *Int. J. Med. Microbial*. **2008**, *298*, 365.
3. Vicini, P.; Zani, F.; Cozzini, P.; Doytchinova, I. *Eur. J. Med. Chem*. **2002**, *37*, 553.
4. Loncle, C.; Brunel, J. M.; Vidal, N.; Dherbomez, M.; Letourneux, Y. *Eur. J. Med. Chem*. **2004**, *39*, 1067.
5. Sridhar, S. K.; Pandeya, S. N.; Stables, J. P.; Atmakuru, R. *Eur. J. Pharm. Sci*. **2002**, *16*, 129.
6. Todeschini, A. R.; Miranda, A. L. P.; Silva, K. C. M.; Parrini, S. C.; Barreiro, E. J. *Eur. J. Med. Chem*. **1998**, *33*, 189.
7. Melnyk, P.; Leroux, V.; Sergheraert, C.; Grellier, P. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 31.
8. Kaymakçıoğlu, B. K.; Rollas, S. *Farmaco* **2002**, *57*, 595.
9. Patole, J.; Sandbhor U.; Padhye, S.; Deobagkar, D. N.; Anson, C. E.; Powell, A. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 51.
10. Geronikaki, A. A.; Lagunin, A. A.; Hadjipavlou-Litina, D. I.; Eleftheriou, P. T.; Filimonov, D. A.; Poroikov, V. V.; Alam, I.; Saxena, A. K. *J. Med. Chem.* **2008**, *51*, 1601.
11. Hrib, N. J.; Jurcak, J. G.; Bregna, D. E.; Burgher, K. L.; Hartman, H. B.; Kafka, S.; Kerman, L. L.; Kongsamut, S.; Roehr, J. E.; Szewczak, M. R.; Woods-Kettelberger, A. T.; Corbett, R. *J. Med. Chem*. **1996**, *39*, 4044.
12. El-Gaby, M. S. A.; El-Hag Ali, G. A. M.; El-Maghraby, A. A.; Abd El-Rahman, M. T.; Helal, M. H. M. *Eur. J. Med. Chem*. **2009**, *44*, 4148.
13. Khan, S. A.; Yusuf, M. *Eur. J. Med. Chem.* **2009**, *44*, 2597.
14. M. de Aquino, T.; Liesen, A. P.; da Silva, R. E. A.; Lima, V. T., Carvalho, C. S.; de Faria, A. R.; de Araújo, J. M.; de Lima, J. D.; Alves, A. J.; de Melo, E. J. T.; Góes, A. J. S. *Bioorg. Med. Chem*. **2008**, *16*, 446.
15. Liu, H. L.; Li, Z.; Anthonsen, T. *Molecules* **2000**, *5*, 1055.
16. Knutsen, L. J. S.; Hobbs, C. J.; Earnshaw, C. G.; Fiumana, A.; Gilbert, J.; Mellor, S. L.; Radford, F.; Smith, N. J.; Birch, P. J.; Burley, J. R.; Ward, S. D. C.; James, L. F. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 662.
17. Wrobel, J.; Jetter, J.; Kao, W., Rogers, J.; Di, L.; Chi, J.; Peréz, M. C.; Chen, G.-C.; Shen, E. S. *Bioorg. Med. Chem.* **2006**, *14*, 5729.
18. Balzarini, J.; Orzeszko-Krzesińska, B.; Maurin, J. K.; Orzeszko, A. *Eur. J. Med. Chem.* **2009**, *44*, 303.
19. Zhou, H.; Wu, S.; Zhai, S.; Liu, A.; Sun, Y.; Li, R.; Zhang, Y.; Ekins, S.; Swaan, P. W.; Fang, B.; Zhang, B.; Yan, B. *J. Med. Chem*. **2008**, *51*, 1242.
20. Pan. B.; Huang, R.; Zheng, L.; Chen, C.; Han, S.; Qu, D.; Zhu, M.; Wei, P. *Eur. J. Med. Chem*. **2011**, *46*, 819.
21. Kavitha, C. V. *Bioorg. Med. Chem.* **2006**, *14*, 2290.
22. Bonde, C. G.; Gaikwad, N. J. *Bioorg. Med. Chem.* **2004**, *12*, 2151.
23. Bondock, S.; Khalifa, W.; Fadda, A. A. *Eur. J. Med. Chem.* **2007**, *42*, 948.
24. Bondock, S.; Khalifa, W.; Fadda, A. A. *Synth. Commun.* **2006**, *36*, 1601.
25. Patel, N. B.; Shaikh, F. M. *Saudi Pharm. J*. **2010**, *18*, 129.
26. Lingampalle, D.; Jawale, D.; Waghmare, R.; Mane, R. *Synth. Commun.* **2010**, *40*(6), 2397.
27. Jaju, S.; Palkar, M.; Maddi, V.; Ronad, P.; Mamledesa, S.; Satyanarayana, D. *Archiv der Pharmazie* **2009**, *342*(12), 723.
28. Lourenço, M. C.da S.; Ferreira, M. de L. M.; Souza, V. N. de; Peralta, M. A.; Vasconcelos, T. R. A.; Henriques, M. das, G. M. O. *Eur. J. Med. Chem.* **2008**, *43*(6), 1344.
29. Khan, M. H. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2007**, *46*(1), 148.
30. Thomas, A. B.; Tupe, P. N.; Badhe, R. V.; Nanda, R. K.; Kothapalli, L. P.; Paradkar, O. D.; Sharma, P. A.; Deshpande, A. D. *Green Chem. Lett. Rev.* **2009**, *2*, 23.
31. Thomas, A. B.; Sharma, P. A.; Nanda, R. K.; Kothapalli, L. P.; Paradkar, O. D.; Deshpande, A. D. *Green Chem. Lett. Rev.* **2011**, *4*(3), 211.
32. Jorgensen, J. H. In *Clinical Microbiology*; Tonover, F. C., Ed.; ASM Press: Washington, DC, 1995; p 1275.