Antimicrobial Evaluation of Imines and Thiazolidinones derived from Ethyl 4-(3-oxoprop-1-ynyl) benzoate

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ABSTRACT
Purpose: The article is aimed to synthesize, characterize and screening the biological activity of a series of 4-(2-methylpyrimidin-4-yl)-N'-4-(4-trifluoromethyl/Nitro/bromo/methoxy/methyl)benzylidene benzohydrazide 4(a-e), and 4-(2-methylpyrimidin-4-yl)-N-(4-oxo-2-(4Trifluoromethyl/Nitro/bromo/methoxy/methyl)phenylthiazolidin-3-yl) benzamide 5(a-e). Methods: The newly synthesized compounds were characterized by elemental analysis and IR, 1H-NMR, 13C NMR and Mass spectral data. The antimicrobial activity of the novel compounds was screened by disk diffusion method. Results: 4a, 5a, 4b and 5be have shown better anti-microbial activity than other compounds of the series.

Keywords: Anti-microbial activity, hydrazide, imines, pyrimidines, thiazolidinone, thioglycolic acid

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INTRODUCTION
It is an established fact that Thiazolidinone, imines show potent antitubercular (1), antimicrobial (2), anticancer (3), antiviral (4), antifungal (4), antibacterial (4) and CCR4 antagonist (5) activities. On the other hand, it is known that imines can be synthesized from ester moieties (6-8), which are precursors for Thiazolidinones (9-10). Due to the activities associated with imines and Thiazolidinone, an attempt was made to generate novel potent antimicrobial imines (4a-e) N'-benzylidene-4-(2-methylpyrimidin-5-yl)benzohydrazide 4(a-e) from ester moiety (2) via synthesis of hydrazide (3) as an intermediate. All the newly synthesized compounds were further characterized and evaluated for antimicrobial activities. Heterocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, and antibiotics, (11,12) hence, they have attracted considerable attention in the design of biologically active molecules [13,14] and advanced organic chemistry [15,16]. Also in the family of heterocyclic compounds nitrogen containing heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes [17]. A totally unsaturated membered six-ring containing nitrogen is known as azine [18] or pyridine (1); with two nitrogen atoms it is known as diazine [19], and with a nitrogen at 1,2-position, it is known as pyridazine, at 1,3-position as Pyrimidine, and at 1,4-position as pyrazine. However, the current review intends to focus on the significance of Pyrimidine class of antimicrobial agents along with clinical and in vitro applications of Pyrimidine derivatives to facilitate the development of more potent as well as effective antimicrobial agents.

Pyrimidine: General Introduction
Pyrimidine is the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six membered rings. Heterocycles containing Pyrimidine moiety are of great interest because they constitute...
an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications [20,21]. Substituted purines and Pyrimidines occur very widely in living organisms and were some of the first compounds studied by the organic chemists [22].

![Scheme](image)

Reagents & Reaction Conditions:
(a) Acetamidine hydrochloride, acetonitrile, sodium carbonate, Microwave Irradiation, 90°C, 1 hr
(b) Hydrazine hydrate, ethanol, reflux, 3 hrs
(c) para substituted aromatic aldehyde, ethanol, reflux, 2 hrs
(d) thioglycolic acid, ZnCl₂, Methanol, reflux, 12 hrs

<table>
<thead>
<tr>
<th>Compound</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
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<td>-NO₂</td>
<td>-Br</td>
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MATERIALS AND METHODS:
All the necessary solvents and chemicals used in the present work were procured from Merck India Pvt. Ltd. (India). The melting points of newly synthesized compounds were determined in open capillary tubes. The IR spectra were recorded (in KBr) on Bruker PCIR instrument, 1H-NMR on Bruker DPX 300 spectrometer, mass spectra on MASPEC (MSW/9629) apparatus and elemental analysis was done on CHN analyzer 240 (Perkin Elmer). Purity of synthesized compounds was checked by TLC on aluminium sheets with silica gel 60 F254 (0.2 mm).

EXPERIMENTAL Section:
General procedure for the preparation of Compound Methyl 4-(2-methylpyrimidin-4-yl) benzoate (Compound 2)
A mixture of methyl 4-(3-oxoprop-1-ynyl) benzoate (0.01 mol) and acetimidamide hydro chloride (0.01 mol) in Dry Aceto Nitrile (10 ml) was taken and Dry Na₂CO₃ (0.02 mol) was added to the above mixture. The resulting mixture was stirred for 0.5 hr
under Micro Wave conditions at 90°C. Reaction progress was monitored by TLC. After completion of reaction, the reaction mass was allowed to stir at room temperature. Then concentrated under reduced pressure by using rota evaporator & Purified by column chromatography (60-120) mesh size silica with elution of 10% Ethyl acetate to get pure yellow solid; yield: 45% mp: 130°c-135°c.

**IR (KBr, cm⁻¹):** 2900(-CH₃ gp), 1720(-CO gp in ester), 1698 (=C-H aromatic), 1160(-C-O-C), 1615 (-C=N)

**H¹-NMR(DMso-d₆, δ, ppm):** 2.4 (1H,S,-CH₃), 3.89(3H,S,CH₃), 8.4(1H, d, J=6.8 Hz), 7.8(1H,d,J=6.8 Hz), 7.8(1H,d,J=7 Hz), 7.9(1H,d,J=7 Hz)

**Found**: C 63.15; H, 5.30; N, 24.55. **Calculated**: C, 62.50; H, 5.30; N, 24.58

**General procedure for the preparation of Compound 4-(2-methylpyrimidin-4-yl)benzohydrazide (Compound 3):**

A mixture of methyl 4-(2-methylpyrimidin-4-yl)benzoate (0.01 mol) in ethanol (10 mL) was Taken and added hydrazine monohydrate 100 percent (47.1 mmol) at room temperature. The reaction mixture was stirred at 80°C for 8 h. The reaction mixture was concentrated under reduced pressure. The solid obtained was filtered off, wash with water, dried and crystallized from methanol to give the compound 3 (white solid) Yield: 85% MP: 160°c-163°c

**IR (KBr, cm⁻¹):** 2948, 3416 (-NH₂), 3200 (-NH), 3040 (=C-H aromatic), 2107 (azide), 1698 (-C=O), 1620 (-C=N)

**H¹-NMR (DMso-d₆, δ, ppm):** 2.4 (3H, S,-CH₃ attached to Pyrimidine ring), 8.0(1H,bs,-NH), 8.2(1H,S,HC=N-), 8.4(1H, d, J=7 Hz), 7.5 (1H, d, J = 7 Hz), 7.9(1H,d,J=8.2 Hz), 7.5(1H,d,J=7.3 Hz), 7.5(1H,d,J=7.3 Hz)

**Yield:** 70% (white solid)

**Melting point:** 130°c to 133°c

**IR (KBr, cm⁻¹):** 3498, 3416 (-NH₂), 3200 (-NH), 3040 (=C-H aromatic), 1698 (-C=O), 1620 (-C=N), 170(acarbonyl carbon)

**MS (m/z):** 384.12 (100.0%)


Elemental Analysis:
Calculated: C, 63.15; H, 4.18; N, 19.38;
Found : C 63.11; H 4.15; N 19.35;
Yield: 70% (white solid)
Melting point: 120°C to 123°C

IR (KBr, cm⁻¹):
3498, 3416 (-NH2), 3200 (-NH), 3040 (=C=N)
Yield: 60% (white solid)

1H-NMR (DMF, δ, ppm):
2.4 (3H, S-CH₃ attached to Pyrimidine ring),
8.0 (1H, s-NH), 8.2 (1H, NH), 8.4 (1H, d), 7.5 (1H, d), 7.9 (1H, d), 8.2 (1H, d), 11.2 (1H, d), 16.2 (1H, d)

13C NMR (DMF, δ, ppm):
24-(CH₃ in Pyrimidine ring), 110-165 (carboxyl carbon), 170 (carbonyl carbon),
MS (m/z): 394.04 (100.0%), 396.04 (97.6%)

Elemental Analysis:
Calculated: C 72.71; H 5.49; N 16.96;
Found : C 72.69; H 5.46; N 16.94

General procedure for synthesis of 4-(2-methylpyrimidin-4-yl)-N-(4-oxo-2-(4-(trifluoromethyl)phenyl)thiazolidin-3-yl)benzamide 5(a-e):
A mixture of Schiff's base (0.01 mol) and thioglycolic acid (0.01 mol) dissolved in dioxane (20 ml), anhydrous zinc chloride (0.01 mol) was added and refluxed for 8 hrs. The reaction was cooled and the resulting solid was washed with 20% sodium bicarbonate solution and recrystallised from absolute alcohol to get compound 5(a-e).

4-(2-methylpyrimidin-4-yl)-N-(4-oxo-2-(4-(trifluoromethyl)phenyl)thiazolidin-3-yl)benzamide 5(a):
Yield: 70% (white solid)
Melting point: 160°C to 165°C

IR (KBr, cm⁻¹): 3498, 3416 (-NH2), 3200 (-NH), 3040 (=C-H aromatic), 1698 (-C=O), 1620 (-C=N)

1H-NMR (DMF, δ, ppm):
2.4 (3H, S-CH₃ attached to Pyrimidine ring),
8.0 (1H, s-NH), 8.2 (1H, NH), 8.4 (1H, d), 7.5 (1H, d), 7.9 (1H, d), 8.2 (1H, d), 11.2 (1H, d), 16.2 (1H, d)

13C NMR (DMF, δ, ppm):
24-(CH₃ in Pyrimidine ring), 110-165 (carboxyl carbon), 170 (carbonyl carbon),
MS (m/z): 458 (100.0%), 459(24.3%)

Elemental Analysis:
Calculated: C 72.71; H 5.49; N 16.96;
Found : C 72.69; H 5.46; N 16.94

General procedure for synthesis of 4-(2-methylpyrimidin-4-yl)-N-(4-oxo-2-(4-(trifluoromethyl)phenyl)thiazolidin-3-yl)benzamide 5(a-e):
A mixture of Schiff's base (0.01 mol) and thioglycolic acid (0.01 mol) dissolved in dioxane (20 ml), anhydrous zinc chloride (0.01 mol) was added and refluxed for 8 hrs. The reaction was cooled and the resulting solid was washed with 20% sodium bicarbonate solution and recrystallised from absolute alcohol to get compound 5(a-e).

4-(2-methylpyrimidin-4-yl)-N-(4-oxo-2-(4-(trifluoromethyl)phenyl)thiazolidin-3-yl)benzamide 5(a):
Yield: 70% (white solid)
Melting point: 160°C to 165°C

IR (KBr, cm⁻¹): 3498, 3416 (-NH2), 3200 (-NH), 3040 (=C-H aromatic), 1698 (-C=O), 1620 (-C=N)
Chemical Formula: C22H17F3N4O2S

Elemental Analysis:
Calculated: C 57.64; H 3.74; N 16.22
Found: C 57.64; H 3.74; N 12.22

4-(2-methylpyrimidin-4-yl)-N-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)benzamide: 5(b)

Yield: 76% (white solid)

Melting point: 110°C-113°C

IR (KBr, cm⁻¹): 3498, 3416 (-NH2), 3200 (-NH), 3040 (=C-H aromatic), 1698 (=C=O), 1620 (C=N), 1188 (C=S).

¹H-NMR (DMSO, δ, ppm):
2.44(3H,S,-CH3 in Pyrimidine ring), 8.4(1H,d,J=8.2Hz), 7.6(1H,d,J=8.2Hz), 8(1H,d,J=7Hz), 7.8(1H,d,J=7Hz), 8(1H,b,-NH), 3.98(1H,d,J=13 Hz, this proton in Thiazolidinone ring), 5.8(1H,S, this proton in Thiazolidinone ring), 3.80(1H,d,J=13Hz, this proton in Thiazolidinone ring), 7.3(1H,d,J=7Hz), 8.4(1H,d,J=7Hz)

¹³C NMR (DMSO, δ, ppm):
24(-CH3 in Pyrimidine ring), 110-165(16 aromatic carbons) 35,64 (this two peaks in Thiazolidinone ring carbons), 175 (carbonyl carbon in Thiazolidinone ring & amide)

Chemical Formula: C21H17BrN4O2S

Elemental Analysis:
Calculated: C 57.91; H 3.91; N 16.06
Found: C 57.91; H 3.91; N 16.06

N-(2-(4-bromophenyl)-4-oxothiazolidin-3-yl)-4-(2-methylpyrimidin-4-yl)benzamide: 5(c)

Yield: 67% (white solid)

Melting point: 120°C-123°C

IR (KBr, cm⁻¹): 3498, 3416 (-NH2), 3200 (-NH), 3040 (=C-H aromatic), 1698 (=C=O), 1620 (C=N), 1188 (C=S).

¹H-NMR (DMSO, δ, ppm):
2.44(3H,S,-CH3 in Pyrimidine ring), 8.4(1H,d,J=8.2Hz), 7.6(1H,d,J=8.2Hz), 8(1H,d,J=7Hz), 7.8(1H,d,J=7Hz), 8(1H,b,-NH), 3.98(1H,d,J=13 Hz, this proton in Thiazolidinone ring), 5.8(1H,S, this proton in Thiazolidinone ring) 3.80(1H,d,J=13Hz, this proton in Thiazolidinone ring), 7.0(1H,d,J=7Hz), 8.0 (1H, d,J=7Hz)

¹³C NMR (DMSO, δ, ppm):
24(-CH3 in Pyrimidine ring), 110-165(16 aromatic carbons), 35,64 (this two peaks in Thiazolidinone ring carbons), 175 (carbonyl carbon in Thiazolidinone ring & amide carbon)

Chemical Formula: C21H17BrN4O2S

MS (m/z):
470(100%), 468(98%)

Elemental Analysis:
Calculated: C 53.74; H 3.65; N 11.94
Found: C 53.72; H 3.63; N 11.92

N-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-4-(2-methylpyrimidin-4-yl)benzamide 5(d):

Yield: 90% (white solid)

Melting point: 150°C-153°C

IR (KBr, cm⁻¹): 3498, 3416 (-NH2), 3200 (-NH), 3040 (=C-H aromatic), 1698 (=C=O), 1620 (C=N), 1188 (C=S).

¹H-NMR (DMSO, δ, ppm):
2.44(3H,S,-CH3 in Pyrimidine ring), 8.4(1H,d,J=8.2Hz), 7.6(1H,d,J=8.2Hz), 8(1H,d,J=7Hz), 7.8(1H,d,J=7Hz), 8(1H,b,-NH), 3.98(1H,d,J=13 Hz, this proton in Thiazolidinone ring), 5.8(1H,S, this proton in Thiazolidinone ring), 7.8(1H,d,J=13Hz, this proton in Thiazolidinone ring), 7.84(1H,d,J=7Hz), 7(1H,d,J=7Hz), 3.83(3H,S,-OCH3)

¹³C NMR (DMSO, δ, ppm):
24 (methyl gp in Pyrimidine ring), 110 to 165 (16 aromatic carbons), 35,64 (this two peaks in Thiazolidinone ring carbons), 175 (carbonyl carbon in Thiazolidinone ring & amide), 55(-OCH3)

MS (m/z):
420.13(100%), 421(24%)

Elemental Analysis:
Calculated: C 62.84; H 4.79; N 13.32
Found: C 62.74; H 4.69; N 13.22

4-(2-methylpyrimidin-4-yl)-N-(4-oxo-2-p-tolythiazolidin-3-yl) benzamide 5(e):

Yield: 56% (white solid)

Melting point: 160°C - 163°C

IR (KBr, cm⁻¹): 3498, 3416 (-NH2), 3200 (-NH), 3040 (=C-H aromatic), 1698 (=C=O), 1620 (C=N), 1188 (C=S).

¹H-NMR (DMSO, δ, ppm):
2.44(3H,S,-CH3 in Pyrimidine ring), 8.4(1H,d,J=8.2Hz), 7.6(1H,d,J=8.2Hz), 8(1H,d,J=7Hz), 7.8(1H,d,J=7Hz), 8(1H,b,-NH), 3.98(1H,d,J=13 Hz, this proton in Thiazolidinone ring), 5.8(1H,S, this proton in Thiazolidinone ring) 3.80(1H,d,J=13Hz, this proton in Thiazolidinone ring), 7.16(1H,d,J=7Hz), 7(1H,d,J=7Hz), 2.3(3H,S, -CH3)

¹³C NMR (DMSO, δ, ppm):
24 (methyl gp in Pyrimidine ring), 170 (carbonyl carbon in amide gp), 110 to 165 (17 aromatic carbons), 35,64 (this two peaks in Thiazolidinone ring carbons),
175 (carbonyl carbon in Thiazolidinone ring), 21 (due to methyl gp which is attached to phenyl ring)

**MS (m/z):** 420.13 (100.0%), 421.13 (24.1%)

**Chemical Formula:** C22H20N4O3S

**Elemental Analysis:**
Calculated: C 62.84; H 4.79; N 13.32
Found: C 62.74; H 4.69; N 13.30

**Biological activity:**
The newly synthesized compounds 4a-e and 5a-e were screened for antibacterial (Staphylococas aurous, Escherichia coli, Pseudomonas aerug- inosa at 37°C) and antifungal (Candida albicans, Asperigillus flavus, Asperigillus fumigatus at 25°C) activities, using nutrient agar and Sabouraudís agar media, respectively, by disk diffusion method at a concentration of 2 mg per mL using DMF as a sol- vent. The results were recorded in duplicate using ampicillin 1 mg/mL and fluconazole 2.5 mg/mL as standards (6, 11) and are given in (Table 1).

### Antimicrobial evaluation of imines and thiazolidinones

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<tr>
<td>4b</td>
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**RESULTS AND DISCUSSION**

**Spectral studies:**
Methyl 4-(2-methylpyrimidin-4-yl)benzoate (2) was synthesized according to the reported procedure\(^{23}\). The reaction of methyl 4-(2-methylpyrimidin-4-yl)benzoate with hydrazine- hydrate in methanol to afford the corresponding (4-(2-methylpyrimidin-4-yl)benzohydrazide (3) as per the reported procedure\(^{24}\) which was reacted with aromatic Para substituted aldehydes in methanol at reflux condition as per the reported procedure\(^{25}\) to afford N’-Substituted benzylidene-4-(2-methylpyrimidin-4-yl)benzohydrazide Compound 4 (a-e) which was reacted with Thioglycolic acid in presence of ZnCl\(_2\) as per the reported procedure\(^{26}\) to afford 4-(2-methylpyrimidin-4-yl)-N-(4-oxo-2-(4-trifluoromethyl)/ Nitro/ Bromo/ Methoxy/ Methyl) phenyl thiazioldin-3-yl benzamide 5(a-e). Elemental analysis, The molecular formulae, structure, also anomeric configuration of the newly Synthesised compounds 4a-e and 5a-e were further conformed and supported by mass, \(^1\)H NMR and IR spectral data, based on occurrence of molecular ion peak of the assigned structures, downfield shifting of protons and different stretching of bands of the compounds. To further support the molecular structure of newly synthesized compounds 4a-e and 5a-e. From antimicrobial evaluation of all the newly synthesized compounds it was seen that each of 4 a-e and 5 a-e compounds possesses significant antibacterial and antifungal activity.

**DISCUSSION**
The structural elucidation of the newly synthesized compounds 2, 3 and 4a-e, 5a-e was done on the basis of spectral and analytical data. The appearance of IR spectral values for newly synthesized compounds near 3250, 2921, 1650, 1765 and 690 cm-1
revealed the presence of NH, CH2, CO (CONH), CO(Thiazolidinone) and C-S groups, respectively. The appearance of 1H-NMR signals for newly synthesized compounds near 2.5, 2.8, 3.4, 5.9, 6.0-7.6, 8.5 and 8.6 ppm were corresponding to the protons of -CH2- CO-, Ar-CH2-, -CH2-S-, -N- CH-S-, aromatic, N=CH and NH groups, respectively. The analytical and spectral data (IR, 1H-NMR, MS) of all the newly synthesized compounds were in full agreement with the proposed structures. The antimicrobial studies of all the newly synthesized compounds 4a-e and 5a-e against freshly cultured strains of S. aureus, E. coli, P. aeruginosa, using sterile Nutrient agar media and C. albicans, A. flavus, A. fumigatus using sterile Sabouraud’s agar media, revealed that all the compounds possess antibacterial and antifungal activities to certain extent. Among the newly synthesized derivatives, compound 4b was found to be more potent than ampicillin when tested against the strains of E. coli. Compounds 4a, 5a and 5b were found to be equipotent to ampicillin when tested on the organisms like E. coli, and P. aeruginosa. Whereas some of the tested compounds 3b, 4a, 4b and 4d have shown good antibacterial and antifungal activity, the remaining compounds have shown moderate activities on tested organisms. After comparing the antimicrobial results of compounds 4a-e and 5a-e, it was concluded that the incorporation of thiazolidinone moiety in the imine derivatives of ethyl 4-(3-oxoprop-1-ynyl)benzoate enhances their antimicrobial activity and also para substitution in Aryl group of thiazolidinones enhances the potency especially in compounds 4a, 5a, and 5b. Further studies to acquire more information about structure activity relationships are in progress in our laboratory.

CONCLUSION
In conclusion a series of new Pyrimidine analogs 4a, 4b, 4c, 4d, 4e and 5a, 5b, 5c, 5d, 5e were synthesized in good yield, characterized by different spectral studies and their anti-microbial activity have been evaluated. Various derivatives of Pyrimidine showed potent anti-microbial activity, like compounds with electron withdrawing groups. Among the synthesized compounds 4a, 5a showed excellent anti-microbial activity when compared to other compounds in the series.

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