

## Synthesis and characterization of new series of imidazolidin-2,4-dione derivatives and its antimicrobial activity

R.SURENDRA KUMAR<sup>1</sup>, A.IDHAYADHULLA<sup>1</sup>,  
A. JAMAL ABDUL NASSER<sup>1\*</sup> and J. SELVIN<sup>2</sup>

<sup>1</sup>P.G & Research Department of Chemistry, Jamal Mohamed College,  
Tiruchirappalli - 620 020 (India).

<sup>2</sup>Department of Microbiology, Bharathidasan University. Tiruchirappalli - 620 024 (India).

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### ABSTRACT

The synthesis of compound (2) was achieved using cyclization method of compound (1) with ethyl chloro acetate and fused sodium acetate. Compound (2) was underwent mannich reaction to give compound (3a-3f). The Chemical structures were elucidated by IR, <sup>1</sup>H NMR, and elemental analysis. The compounds (2) and (3a-3f) have been screened for in vitro antimicrobial action against various strains of bacterial and fungi.

**Key words:** Imidazolidin-2, 4-dione, mannich base, antimicrobial activity.

### INTRODUCTION

Imidazolidin-2,4-dione derivatives are significant biological and pharmacological properties of anti-inflammatory<sup>1</sup>, antimicrobial activity<sup>2</sup> (antifungal, antibacterial), anticonvulsant<sup>3</sup>.

Number of literature methods are indicated that various synthetic methods used to prepared imidazolidin-2,4-dione and their biological screening<sup>4-6</sup>. Recent literature methods are indicated that aromatic benzene present in third position of imidazolidin-2, 4-dione ring and it was involved mannich base reactions<sup>7</sup>. Basically mannich base were found to potential of biological activities such as antibacterial<sup>8</sup>, antifungal<sup>9</sup>.

Major role of this study, a new series of mannich base derivatives (3a-3f) was prepared from imidazolidin-2,4-dione with 4-substituted benzaldehyde and semicarbazone the synthesized compounds (2) and (3a-3f) were compared the level of antimicrobial action.

### MATERIAL AND METHODS

Melting points were recorded in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr on a FT-IR shimadzu 8201pc (4000-400 cm<sup>-1</sup>) and <sup>1</sup>H NMR on a Bruker DRX-300 MHz. Elemental analyses (C, H, N, and S) were undertaken using an Elementer analyzer model vario EL III. The purity of the compounds was checked by thin layer chromatography (TLC) with silica gel plates.

#### Synthesis of 2-(pyridin-2-ylmethylidene)hydrazinecarboxamide (1)

A mixture of pyridine-2-aldehyde (0.1 mol), semicarbazide (0.1 mol) in ethanol (10 ml), and the reaction mixture was heated and reflux for 4 hr on water-bath. The reaction mixture was cooled, and poured in to crushed ice, the solid was filtered, and recrystallised from suitable alcohol.

IR (KBr, cm<sup>-1</sup>): 3374(NH), 3285(NH<sub>2</sub>), 3021(aromatic CH stretching), 1723(C=O), 1623(C=N); <sup>1</sup>H NMR-(DMSO-d<sub>6</sub>, δ(ppm)): 10.55

(s,1H,NH), 10.11(s,1H,CH=N), 8.59-7.23 (m,4H, pyridyl), 6.20(s,2H, NH<sub>2</sub>),

#### Synthesis of 3-[[pyridin-2-ylmethylene]amino]imidazolidine-2,4-dione (2)

A mixture of pyridine-2-carbaldehyde semicarbazone (0.01mol) and ethylchloroacetate (0.01mol) and fused sodium acetate (0.03 mol) in ethanol, the reaction mixture was heated under reflux for 4 hr on water-bath. The reaction mixture was cooled, and poured in to crushed ice, the solid was filtered, and recrystallised from ethanol.

IR (KBr, cm<sup>-1</sup>): 3342.11(NH), 3234 (aromatic C-H stretching), 1695.82(C=O, in imidazolidine ring), 1631.42(C=N cm<sup>-1</sup>); <sup>1</sup>HNMR-(DMSO-d<sub>6</sub>, δ (ppm)): 8.67 – 7.67 (d, 4H, pyridyl), 7.42 (s, 1H, CH=N), 6.01(s,1H, NH in imidazolidin ring), 3.84 (s, 2H, CH<sub>2</sub>N in imidazolidin ring);

#### Elemental analysis

Calculated for C<sub>9</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub>: C, 52.94; H, 3.95; N, 27.44. Found: C, 52.87; H, 3.91; N, 27.40%

#### 2-[(2,4-dioxo-3-[[pyridin-2-ylmethylene]amino]imidazolidin-1-yl)(phenyl)methyl]hydrazinecarboxamide (3a)

To prepare the solution of Compound (2) (0.1mol), 4-substitutedbenzaldehyde (0.01 mol) and thiosemicarbazone (0.01 mol) in 25 ml of absolute ethanol, the reaction mixture was heated under reflux for 5hr. The reaction mixture was cooled and poured in to ice-cold water. The solid was filtrate and recrystallised from absolute ethanol. Using the above procedure was followed for all the remaining compounds (3b-3f).

IR (KBr,cm<sup>-1</sup>): 3301(NH), 3285.32( NH<sub>2</sub> ), 3021( aromatic C-H stretching ), 1723(C=O), 1623(C=N), 1493(C=S), 1092(N-CH-N); <sup>1</sup>HNMR-(DMSO-d<sub>6</sub>, δ(ppm)): 10.54(s, 1H,-CH=N-), 9.53(s, 2H, NH<sub>2</sub>), 7.85-7.64(m, 4H, pyridyl), 7.44(s, 2H, NH<sub>2</sub>), 6.69(s,1H, N-CH-N), 4.22 ( s, 2H, H<sub>2</sub>C-N ), 2.31 (s,1H, NH-CS);

#### Elemental analysis

Calculated for C<sub>17</sub> H<sub>17</sub> N<sub>7</sub> O<sub>3</sub>: C, 53.20; H, 4.43; N, 25.55; S, 8.34;

Found: C, 53.15; H, 4.38; N, 25.59; S, 8.37 %.

#### Synthesis of 2-[(4-chlorophenyl)(2,4-dioxo-3-[[pyridin-2-ylmethylene]amino]imidazolidin-1-yl)methyl]hydrazinecarboxamide (3b)

IR (KBr, cm<sup>-1</sup>): 3485(NH<sub>2</sub>), 3021(aromatic C-H stretching), 2974(NH), 1728.71(C=O), 1623.87(C=N), 1424.80(C=S), 1021.33(N-CH-N), 830(C-Cl); <sup>1</sup>HNMR-(DMSO-d<sub>6</sub>, δ (ppm)): 10.51 ( s, 1H, -CH=N- ), 9.58 (s, 2H, NH<sub>2</sub>), 7.78-7.69 ( m, 4H, pyridyl ), 7.37( s, 2H, NH<sub>2</sub>), 6.54( s, 1H, -CH-), 4.17( s, 2H, H<sub>2</sub>C-N ), 2.23 (s, 1H, NH-CS);

Elemental analysis: Calculated for C<sub>17</sub> H<sub>16</sub>Cl N<sub>7</sub>O<sub>3</sub>S: C, 48.81; H, 3.82; N, 23.45; S, 7.65; Found: C, 48.88; H, 3.85; N, 23.40; S, 7.61 %.

Synthesis of 2-[(2,4-dioxo-3-[[pyridin-2-ylmethylene]amino]imidazolidin-1-yl)

#### (4-hydroxyphenyl)methyl]hydrazinecarboxamide (3c)

IR (KBr,cm<sup>-1</sup>): 3328 (NH), 3281(NH<sub>2</sub>), 3011(aromaticC-Hstretching), 1737 (C=O), 1638(C=N), 1472(C=S), 1450(OH), 1098(N-CH-N); <sup>1</sup>HNMR-(DMSO-d<sub>6</sub>, δ(ppm)): 11.96 ( s, 1H,-OH), 10.41 (s,1H,-CH=N-), 9.47 (s, 2H, NH<sub>2</sub>), 7.42-7.12 (m, 4H, pyridyl), 6.61(s,1H, -CH-), 4.20 ( s, 2H, H<sub>2</sub>C-N ), 2.38 (s, 1H, NH-CS);

#### Elemental analysis

Calculated for C<sub>17</sub>H<sub>17</sub>N<sub>7</sub>O<sub>3</sub>S:C,51.07;H, 4.25;N,24.53; S, 8.01;

Found: C, 51.12; H, 4.29; N, 24.59; S, 8.09 %.

#### Synthesis of 2-[(2,4-dioxo-3-[[pyridin-2-ylmethylene]amino]imidazolidin-1-yl)(4-methoxyphenyl)methyl]hydrazinecarboxamide (3d)

IR (KBr, cm<sup>-1</sup>): 3328 (NH<sub>2</sub>), 3071(aromatic C-H stretching), 1720(C=O), 1637(C=N), 1487 (C=S), 1087 (N-CH-N); <sup>1</sup>HNMR-( DMSO-d<sub>6</sub>, δ(ppm)): 10.32(s,1H, -CH=N-), 9.64 (s, 2H, NH<sub>2</sub>), 7.75-7.41 (m, 4H, pyridyl), 7.47 (s, 2H, NH<sub>2</sub>), 6.72 (s,1H, -CH-), 4.28 ( s, 2H, H<sub>2</sub>C-N ), 4.12( s, 3H, CH<sub>3</sub>), 2.35 ( s, 1H, NH-CS );

#### Elemental analysis

Calculated for C<sub>18</sub>H<sub>19</sub>N<sub>7</sub>O<sub>3</sub>S: C, 52.24; H, 4.59; N, 23.70; S, 7.73;

Found: C, 52.27; H, 4.55; N, 23.65; S, 7.77 %.

**2 - [(2,4-dioxo-3-[[pyridin-2-ylmethylene]amino]imidazolidin-1-yl) (4-nitrophenyl) methyl] hydrazinecarboxamide (3e)**

IR (KBr,  $\text{cm}^{-1}$ ): 3334 ( $\text{NH}_2$ ), 3021 (aromatic C-H stretching), 2974 (NH), 1732 (C=O), 1623 (C=N), 1530 ( $\text{NO}_2$ ), 1490 (C=S), 1080 (N-CH-N);  $^1\text{H}$ NMR-(DMSO- $d_6$ , $\delta$ (ppm)): 10.47 (s, 1H, -CH=N-), 9.61 (s, 2H,  $\text{NH}_2$ ), 7.57-7.30 (m, 4H, pyridyl), 7.42 (s, 2H,  $\text{NH}_2$ ), 6.62 (s, 1H, -CH-), 4.20 (s, 2H,  $\text{H}_2\text{C-N}$ ), 2.31 (s, 1H, NH-CS);

**Elemental analysis**

Calculated for  $\text{C}_{17}\text{H}_{16}\text{N}_8\text{O}_4\text{S}$ : C, 47.61; H, 3.73; N, 26.14; S, 9.46;

Found: C, 47.66; H, 3.77; N, 26.18; S, 9.41 %.

**Synthesis of 2-[(2,4-dioxo-3-[[pyridin-2-ylmethylene]amino]imidazolidin-1-yl) (4-dimethylamino) methyl] hydrazinecarboxamide (3f)**

IR (KBr,  $\text{cm}^{-1}$ ): 3341 ( $\text{NH}_2$ ), 3214 (NH), 3021 (aromatic C-H stretching), 1721 (C=O), 1627 (C=N), 1457 (C=S), 1093 (N-CH-N);  $^1\text{H}$ NMR-(DMSO- $d_6$ , $\delta$ (ppm)): 9.98 (s, 1H, -CH=N-), 9.47 (s, 2H,  $\text{NH}_2$ ), 7.61-7.47 (m, 4H, pyridyl), 7.47 (s, 2H,  $\text{NH}_2$ ), 6.77 (s, 1H, -CH-), 4.32 (s, 2H,  $\text{H}_2\text{C-N}$ ), 2.41 (s, 1H, NH-CS), 1.82 (s, 6H,  $-\text{N}(\text{CH}_3)_2$ );

**Elemental analysis**

Calculated for  $\text{C}_{19}\text{H}_{22}\text{N}_8\text{O}_2\text{S}$ : C, 53.45; H, 5.15; N, 26.20; S, 7.50; Found: C, 53.49; H, 5.19; N, 26.24; S, 7.47 %.

**Antimicrobial activity****In vitro anti bacterial activity**

Compounds (2), (3a-3f) were evaluated for their *in vitro* antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, by agar dilution method<sup>10,11</sup> were performed using Mueller- Hinton agar (Hi-media) each compounds and standard were tested at a concentration of 100  $\mu\text{g}/\text{ml}$  in DMSO, the zone of inhibition were measured after 24hr incubation at 37°C. After the incubation period the diameter of clear zone around each well were measured in mm, clearing zone of variable size are visible the well of each compound nitrofurantoin was chosen as a standard of antibacterial activity.

**In vitro anti fungal activity**

The compounds were evaluated for their *in vitro* antifungal activity of *Aspergillus niger*, *Candida albicans*, *Cryptococcus neoformans*, *A.fumigatus* using an agar dilution method<sup>12</sup>. With sabouraud's dextrose agar (Hi-Media). Each compounds and standard were tested at a concentration of 100  $\mu\text{g}/\text{ml}$  in DMSO. The zone of inhibition were measured incubated at 37°C for 24h inhibition zone were measured in mm. Clotrimazole was used as a standard.

**RESULTS AND DISCUSSION**

In the present work 3-[[1-pyridin-2-ylmethylene] amino]-2-thioxoimidazolidin-4-one (2) was prepared for cyclization method, pyridine-2-carbaldehyde thiosemicarbazone with ethyl chloroacetate and fused sodium acetate with method described in the literature<sup>7</sup>. The mannich base condensation of compound (3a-3f) with 4-substituted aromatic aldehyde and thiosemicarbazone resulted in the formation of final compound.

Compound (2) and compounds (3a-3f) (Scheme 1), physical dates are given in (Table 1). The structures of these compounds were confirmed by IR,  $^1\text{H}$ NMR, and elemental analysis.

IR spectrum of compound 2 showed absorption bands at 1695 and 1631  $\text{cm}^{-1}$  corresponding to the C=O and HC=N groups respectively.  $^1\text{H}$ NMR spectral data of the compound 2 showed presence of  $\text{CH}_2\text{N}$  Protons of the

**Table 1: Characterization data of compounds (2), (3a-3f)**

Comp. no	R	mp(°C)	Yield %
1	-	152	65
2	-	163	60
3a	H	172	51
3b	Cl	190	55
3c	OH	201	50
3d	$\text{NO}_2$	195	55
3e	$\text{OCH}_3$	200	58
3f	$\text{N}(\text{CH}_3)_2$	210	60

imidazolidin ring appeared at  $\delta$  3.84, while CH=N protons appeared at  $\delta$  7.42 and respectively.

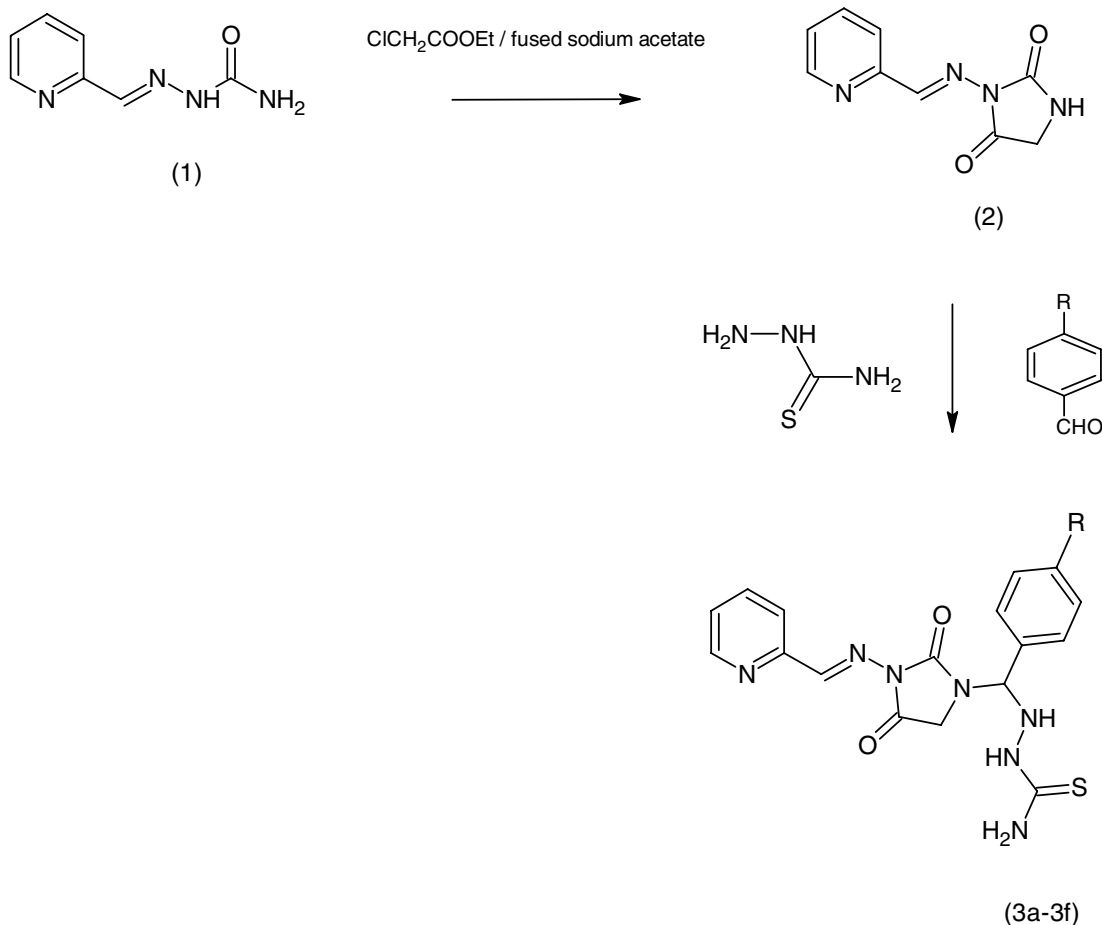
IR spectrum of the compound (3a-3f) showed absorption bands at 1737 - 1720  $\text{cm}^{-1}$  and 1424 - 1493  $\text{cm}^{-1}$  corresponding to the C=O and C=S groups respectively. The N-C-N stretching frequency at 1098 - 1021  $\text{cm}^{-1}$  clearly indicates the formation of mannich base reaction.  $^1\text{H}$ NMR spectral data of the compound (3a-3f) showed the absence of  $\text{CH}_2\text{N}$  protons appeared at  $\delta$  4.17 - 4.32 regions, while N-CH-N proton appeared at  $\delta$  6.61-6.72 ppm respectively it is clearly indicates that mannich base derivatives.

#### Anti microbial screening

Compounds (2), (3a-3f) were screened for

antibacterial activity against *S. aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia*. The comparison of the compounds (2) and (3a-3f), compounds (3a-3f) has highly active than the compound 2. The compound (3b) containing 4-Cl-phenyl group has highly active against *Enterococcus faecalis* compared with nitrofurantoin.

Compounds (2), (3a-3f) were exhibit antifungal activity against *A. niger*, *C. albicans*, *A. fumigatus*, *Cryptococcus neoformans*. The comparison of the compounds (2), (3a-3f) was found to exhibit compounds (3a-3f) has highly active against all fungal organisms. The compound (3e) containing 4- $\text{NO}_2$ -phenyl group has highly active against *A. fumigatus* compared with clotrimazole.



Scheme 1: Synthesis of mannich base imidazolidin-2, 4-dione derivatives

**Table 2: Antibacterial activity of compounds (2), (3a-3f) Zone of inhibition (mm)**

Compounds	<i>S.aureus</i>	<i>E.faecalis</i>	<i>P. aeruginosa</i>	<i>K. pneumoniae</i>
2	7	-	14	-
3a	12	-	16	-
3b	13	22	12	6
3c	18	8	10	8
3d	16	-	18	-
3e	9	-	17	-
3f	10	-	-	-
Nitrofurantoin	15	17	23	20

Indicates above bacteria's were resistant to the compound concentration (100µg/ml).

Nitrofurantoin is used as the standard

**Table 3: Antifungal activity of compounds (2),(3a-3f) Zone of inhibition (mm)**

Compounds	<i>A. niger</i>	<i>C.albicans</i>	<i>A.fumigatus</i>	<i>Cr.neoformans</i>
2	-	12	-	-
3a	12	13	11	10
3b	6	18	6	6
3c	13	14	12	11
3d	6	18	6	6
3e	5	-	20	5
3f	8	10	5	9
Clotrimazole	25	15	15	22

Indicates above fungal were resistant to the compound concentration (100µg/ml).

Clotrimazole is used as the standard.

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