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Synthesis and Biological Activities of New Series of Imidazolidin-2,4-dione Derivatives

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3-{[2-Furylmethylene]amino}imidazolidine-2,4-dione (**2**) was synthesized by compound **1**, ethylchloroacetate and fused sodium acetate involved in cyclization method. A series of imidazolidin-2,4-dione derivatives (**3a-3f**) were synthesized by composition of compound **2** with 4-substituted benzaldehyde and hydrazine hydrate from Mannich base method. The chemical structures of the compounds were conformed by IR, ^{1}H NMR and elemental analysis. The synthesized compounds have been tested *in vitro* for their antimicrobial action against various strains of bacterial and fungi organisms.

Key Words: Imidazolidin-2,4-dione, Mannich base, Antimicrobial activity.

INTRODUCTION

Imidazole, imidazolidin-2,4-dione, imidazolidin-2-thioxo-4-one and their heterocyclic derivatives represent an interesting class of compounds which possess a wide range of biological activities, such as antiinflammatory[1], antimicrobial[2] (antifungal, antibacterial) and anticonvulsant[3] activities. Most of the work have been carried out substitution at the 3 and 5 position of the imidazolidin derivatives and investigated the antimicrobial activity[4-7]. It is found in literature survey that the imidazolidin-2,4-diones have been biologically significant compounds[8]. Present work involve in constitution of modified imidazolidi-2,4-dione ring in first position NH in Mannich base condensation. Basically Mannich base derivatives were found to potential of antibacterial[9] and antifungal[10] activities. Taking literature survey as a base of synthesized imidazolidin derivatives (**3a-3f**) and screened the level of antimicrobial action. Imidazolidin derivatives (**3a-3f**) were prepared by the procedure described in **Scheme-II**.

EXPERIMENTAL

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^{-1}) and ^{1}H NMR on a Bruker DRX-300 MHz. Elemental analysis (C, H, N and S) were undertaken using an elemental analysis model vario EL III. The purity of the compounds was checked by thin layer chromatography with silica gel plates.

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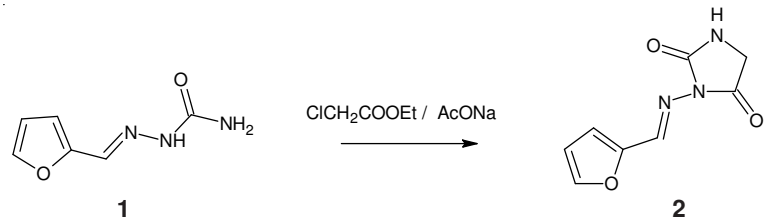
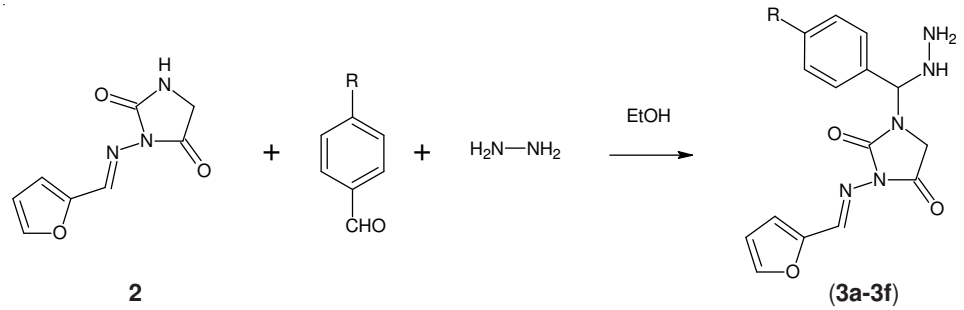


Scheme-I: Synthesis of imidazolidin-2,4-dione



Scheme-II: Synthesis of imidazolidin-2,4-dione Mannich base derivatives

General procedures

3-{[2-Furylmethylene]amino}imidazolidine-2,4-dione (2): A mixture of the compound **1** (0.01 mol), ethyl chloro acetate (0.01 mol) and fused sodium acetate (0.1 mol) in ethanol was heated and reflux for 2 h. The reaction mixture was allowed to cool to room temperature and poured in an ice water. The solid was obtained and collected by filtration. The solid was purified by crystallization from suitable alcohols. IR (KBr, ν_{max}, cm^{-1}): 3348 (NH), 3034 (aromatic C-H- *str.*),1628(C=O), 1517 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 8.27 (s, 1H, HC-N), 6.17 (s, 1H, NH in imidazolidin ring), 6.43-6.72 (d, 2H, furyl), 3.71 (s.1H, CH_2N), elemental analysis (%): calculated for $C_8H_7N_3O_3$: C, 49.70; H, 3.62; N, 21.74; Found: C, 49.74; H, 3.66; N, 21.77.

Synthesis of series of compounds (3a-3f)

3-{[2-Furylmethylene]amino}-1-[hydrazino(phenyl)methyl]imidazolidine-2,4-dione (3a): A mixture of the compound **2** (0.1 mol), benzaldehyde (0.1 mol) and hydrazine hydrate (0.1 mol) in ethanol was heated under reflux for 2 h. After 2 h, the reaction mixture was allowed to cool room temperature and poured in an ice water. The solid was obtained and collected by filtration. The solid was purified by crystallization from suitable alcohol. Using the above procedure was followed for the entire remaining compound **3b-3f**. IR (KBr, ν_{max}, cm^{-1}): 3368 (NH), 3287 (NH_2), 3034 (aromatic C-H- *str.*), 1621(C=O), 1520 (C=N); ^{1}H NMR(DMSO-d_6), δ (ppm): 8.21 (s, 1H, HC-N), 7.17-7.41 (m, 5H, phenyl), 6.41-6.87 (d, 2H, furyl), 4.12 (s, 1H, CH_2-N), 6.23 (s, 1H, CH), 2.24 (s, 2H, NH_2), 2.01 (s, 1H, NH), elemental analysis (%): calculated for $C_8H_{15}N_5O_3$: C, 57.45; H, 4.78; N, 22.34; Found: C,

57.48; H, 4.80; N, 22.36.

1-[(4-Chlorophenyl)(hydrazino)methyl]-3-{[2-furylmethylene]amino}-imidazolidine-2,4-dione (3b): IR (KBr, ν_{max}, cm^{-1}): 3084 (NH), 3034 (aromatic C-H-*str.*), 1621 (C=O), 1520 (C=N), 1493 (C=S); 837 (C-Cl); ^{1}H NMR (DMSO-d_6), δ (ppm): 8.28 (s, 1H, HC-N), 7.26-7.43 (m, 5H, phenyl), 6.52-6.93 (d, 2H, furyl), 6.01 (s, 1H, CH), 4.05 (s, 1H, CH_2-N), 2.2 (s, 2H, NH_2), 2.0 (s,1H,NH), elemental analysis (%): calculated for $C_{15}H_{14}ClN_5O_3$: C, 51.76; H, 4.02; N, 20.12; found (%): C, 51.79; H, 4.05; N, 20.15.

3-{[2-Furylmethylene]amino}-1-[hydrazino(4-hydroxyphenyl)methyl]-imidazolidine-2,4-dione (3c): IR (KBr, ν_{max}, cm^{-1}): 3342 (NH), 3241 (NH_2), 3027 (aromatic C-H- *str.*), 1465 (OH) 1627 (C=O), 1523 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 9.43 (s, 1H, OH-C), 8.31 (s, 1H, HC-N), 7.21-7.37 (m, 5H, phenyl), 6.41-6.90 (d, 2H, furyl), 6.14 (s, 1H, CH), 4.11 (s, 1H, CH_2-N), 2.2 (s, 2H, NH_2), 2.10 (s, 1H, NH); elemental analysis (%): calculated for $C_{15}H_{15}N_5O_4$: C, 54.65; H, 4.55; N, 21.25; found: C, 54.68; H, 4.58 N, 21.28.

3-{[2-Furylmethylene]amino}-1-[hydrazino(4-methoxyphenyl)methyl]-imidazolidine-2,4-dione (3d): IR (KBr, ν_{max}, cm^{-1}): 3308 (NH), 3217 (NH_2), 3021 (aromatic C-H- *str.*), 1618 (C=O), 1548 (NO_2), 1527 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 8.26 (s, 1H, HC-N), 7.20-7.38 (m, 5H, phenyl), 6.45-6.87 (d, 2H, furyl), 6.01 (s, 1H, CH), 4.06 (s, 1H, CH_2-N), 2.29 (s, 2H, NH_2), 2.12 (s, 1H, NH); elemental analysis (%): calculated for $C_{16}H_{17}N_5O_4$: C, 55.92; H, 4.95; N, 20.38; found: C, 55.95; H, 4.99; N, 20.40.

3-{[2-Furylmethylene]amino}-1-[hydrazino(4-nitrophenyl)methyl]-imidazolidine-2,4-dione (3e): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH), 3265 (NH_2), 3034 (aromatic C-H- *str.*), 1621 (C=O), 1520 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 9.50 (s, 3H, OH_3C-C), 8.25 (s, 1H, HC-N), 7.28-7.57(m, 5H, phenyl), 6.61-6.73 (d, 2H, furyl), 6.13 (s, 1H, CH), 4.12 (s, 1H, CH_2-N), 2.25 (s, 2H, NH_2), 2.13 (s, 1H, NH); elemental analysis (%): calculated for $C_{15}H_{14}N_6O_5$: C, 50.23; H, 3.90; N, 23.44; found: C, 50.28; H, 3.93; N, 23.47.

1-{[4-(Dimethylamino)phenyl](hydrazino)methyl}-3-{[2-furylmethylene]-amino}imidazolidine-2,4-dione (3f): IR (KBr, ν_{max}, cm^{-1}): 3391 (NH), 3214 (NH_2), 3034 (aromatic C-H- *str.*), 1638 (C=O), 539 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 8.32 (s, 1H, HC-N), 7.46-7.28 (m, 5H, phenyl), 6.92-6.72 (d, 2H, furyl), 6.12 (s, 1H, CH), 4.16 (s, 1H, CH_2-N), 2.82 (s, 6H, -$N(CH_3)_2$), 2.30 (s, 2H, NH_2), 2.09 (s, 1H, NH); elemental analysis (%): calculated for $C_{17}H_{20}N_6O_3$: C, 57.24; H 5.61; N, 23.57; found: C, 57.27; H, 5.64; N, 23.60.

Antimicrobial activity

***In vitro* antibacterial 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[11,12] were performed using Mueller-Hinton agar (Hi-media) each compounds and standard were tested at a concentration of 100 µg/mL in DMSO. The zone of inhibition were measured after 24 h incubation at 37 ºC. 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. Ciprofloxacin was chosen as a standard of antibacterial activity.

In vitro antifungal activity: The compounds **2**, **3a-3f** were evaluated for their *in vitro* antifungal activity of *Aspergillus niger, Candida albicans, Cryptococcus neoformans, Microsporum audouinii* using an agar dilution method[13]. With Sabouraud's dextrose agar (Hi-Media). Each compounds and standard were tested at a concentration of 100 µg/mL in DMSO. The zone of inhibition were measured incubated at 37 ºC for 24 h inhibition zone were measured in mm. Clotrimazole was used as a standard.

RESULTS AND DISCUSSION

The condensation of furyl-2-aldehyde react with semicarbazide resulted in the formation of compound **1** method was followed by literature[14]. Compound **2** was synthesized by the reaction of compound **1** with ethylchloroacetate in presence of fused sodium acetate with the method described in the literature[15]. The physical characterization data of imidazolidin derivatives (**2**) (**3a-3f**) are given in Table-1. The formation of imidazolidin ring and Mannich base derivatives was conformed by IR, ^{1}H NMR and elemental analysis.

TABLE-1
CHARACTERIZATION DATA OF COMPOUNDS **2** AND **3a-3f**

Compd.	R	m.p. (ºC)	Yield (%)
2	-	153	59
3a	-H	156	43
3b	-Cl	170	47
3c	-OH	131	44
3d	$-NO_2$	155	43
3e	$-OCH_3$	190	51
3f	$-N(CH_3)_2$	128	49

TABLE-2
ANTIBACTERIAL ACTIVITY OF COMPOUNDS **2** AND **3a-3f**
ZONE OF INHIBITION MEASURED (mm)

Compd.	*S. aureus*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
2	-	6	7	-
3a	6	6	-	8
3b	21	15	13	-
3c	15	7	16	6
3d	13	12	7	8
3e	-	15	9	-
3f	9	17	16	-
Standard	22	27	32	19

Indicates bacteria are resistant to the compound (100 µg/mL).
Ciprofloxacin is used as the standard (100 µg/mL).

TABLE-3
ANTIFUNGAL ACTIVITY OF COMPOUNDS **2** AND **3a-3f**
ZONE OF INHIBITION MEASURED (mm)

Compd.	*A. niger*	*C. albicans*	*Cr. Neoformans*	*M. audouinii*
2	15	12	6	8
3a	19	20	12	17
3b	13	17	8	-
3c	24	18	9	-
3d	16	17	16	7
3e	18	19	7	-
3f	10	16	23	9
Standard	22	24	26	25

Indicates fungal are resistant to the compound (100 µg/mL).
Clotrimazole is used as the standard (100 µg/mL).

The IR septum of compound **2** showed absorption bands at 3348, 1517, 1628 cm^{-1} corresponding to the NH, C=N and C=O group receptivity. The ^1H NMR spectrum of the compound **2** showed a broad singlet at δ 3.71 corresponding to CH_2N protons, a sharp singlet observed at δ 8.27 is attributed to the CH=N protons.

The IR spectrum of the compound **3a-3f** showed an absorption band at 1517-1539, 3321-3368 and 3287-3201 cm^{-1} corresponding to the C=N, NH and NH_2. The ^1H NMR spectrum compound **3a-3f** showed broad singlet at 4.06-4.16 cm^{-1} corresponding to CH_2N and important peak of conformed by mannich base compound **3a-3f** singlet at δ 6.01 to 6.23 corresponding CH protons receptivity.

A total of 7 compounds were screened for *in vitro* antibacterial and antifungal activity. It was found some compound showed significant and equipotent activity than the standard. Compound **3b** showed equipotent activity against *S. aureus* and other compound was less active compared with ciprofloxacin at 100 µg/mL in antibacterial screening. Compound **3c** showed highly activity against *A. niger*, compound **3f** showed equipotent activity against *Cr. neoformans*,. Other compounds have less active compared with clotrimazole at 100 µg/mL in antifungal screening.

Conclusion

The new series of imidazolidine-2,4-dione derivative (**3a-3f**) was synthesized and screened the level of antimicrobial action. Compound **3b** has equipotent activity against *S. aureus* compared with ciprofloxacin in antibacterial screening. Compound **3c** has highly activity against *A. niger*; compound **3f** has equipotent activity against *Cr. neoformans*, compared with clotrimazole in antifungal screening.

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