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Evaluating one-pot synthesis of 3,5-substituted hydantoins and their biological studies

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ABSTRACT

The present paper describes studies on the synthesis of 3,5-substituted imidazolidine-2,4-dione via Mannich reaction between various secondary amines and hydantoin derivatives. For all compounds NOE (Nuclear Overhauser Effect) NMR spectra were deliberate in order to confirm additionally the position of the substituent in the imidazolidine-2,4-dione ring. Some physiochemical and electronic properties of the compounds were determined in order to found the resemblance between the synthesized and reference compounds. All the compounds were also characterized by ^{13}C NMR, FT-IR and LC/MS mass spectrum. All the newly synthesized compounds were screened for their in vitro antimicrobial activity and many of them found to show similar activity to the standard drug with different microorganisms.

Keywords: Hydantoin; Secondary Amines; Mannich Reaction; Antimicrobial Studies.

INTRODUCTION

A hydantoin (imidazolidine-2,4-dione) skeleton[1] is an important structural motif found in a number of pharmaceutically active compounds,[2] such as phenytoin and fosphenytoin which are in practical use for the treatment of epilepsy. In addition, substituted hydantoins act as valuable intermediates for the synthesis of enantiomerically pureamino acids through dynamic kinetic resolution using hydantoinase biocatalysis.[3] Therefore, the development of efficient methods for rapid construction of hydantoin skeletons from simple and inexpensive starting materials is highly desired. The hydantoin nucleus [4] has many pharmacological effects1 and is found in several clinically important medicines (e.g., nilutamide, [5] phenytoin[6]). Hydantoins also serve as useful intermediates for the preparation of non-natural amino acids via chemical1 or enzymatic hydrolysis.[7] Of existing methods to hydantoins,[4,8] the Bucherer–Bergs reaction provides perhaps the best method for their preparation.[9,10]

The Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group with formaldehyde and ammonia or any primary or secondary amine. The final product is a β-amino-carbonyl compound also known as a Mannich base. Reactions between aldimines and α-methylene carbonyls are also considered Mannich reactions becausevthese imines form between amines and aldehydes. The Mannich reaction is an example of nucleophilic addition ofvan amine to a carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which reacts in the second step in a nucleophilic addition with a compound containing an acidic proton. The Mannich reaction is alsoconsidered a condensation reaction. The Mannich reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides,

antibiotics, and alkaloids (e.g. tropinone). Other applications are in agro chemicals such as plant growth regulators, paint and polymer chemistry,catalysts and cross linking. The Mannich reaction is also used in the synthesis of medicinal compounds e.g. rolitetracycline (Mannich base of tetracycline), fluoxetine (antidepressant) and tolmetin (anti-inflammatory drug). Literature survey reveals that some. Mannich bases of substituted aminophenol and acetophenone possess broad spectrum biological activities, which include Antineoplastic [11], Antibacterial [12,13] and Antifungal [14,15], Anti HIV [16,17], Anticancer [18,19,20], Tuberculosis [21], Neurotoxicity [22], Vasorelaxant [23], Anti inflammatory [24], Antimalarial [25], Analgesic [26,27].

Thus, looking to the wide applications, the present communication comprises the mild one-pot conversion of hydantoin to the corresponding 3,5-disubstituted imidazolidine-2,4-dione with high yields. Such a transformation would be particularly useful for medicinal chemists since it would give them direct access to a useful bioisostere of the ester in a single chemical transformation.

MATERIALS AND METHODS

The elemental analyses were performed by Vario EL CHN elemental analyzer. The FT-IR spectra were recorded on Perkin Elmer Spectrum GX spectrophotometer using KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz instrument using DMSO-d6 as solvent. The MS-CI spectrum of were recorded on Shimadzu LC–MS 2010 eV spectrometer in acetonitrile. The melting points were checked by standard open capillary method and are uncorrected.

Synthesis
All required chemicals were purchased commercially from Hi-Media Laboratories Pvt. Ltd., India, and were used without further purification. The synthetic path is shown in Scheme 1.

Imidazolidine-2,4-dione (a,b)
Various derivatives of imidazolidine-2,4-dione have been prepared by conversational method and characterized by various spectral method.

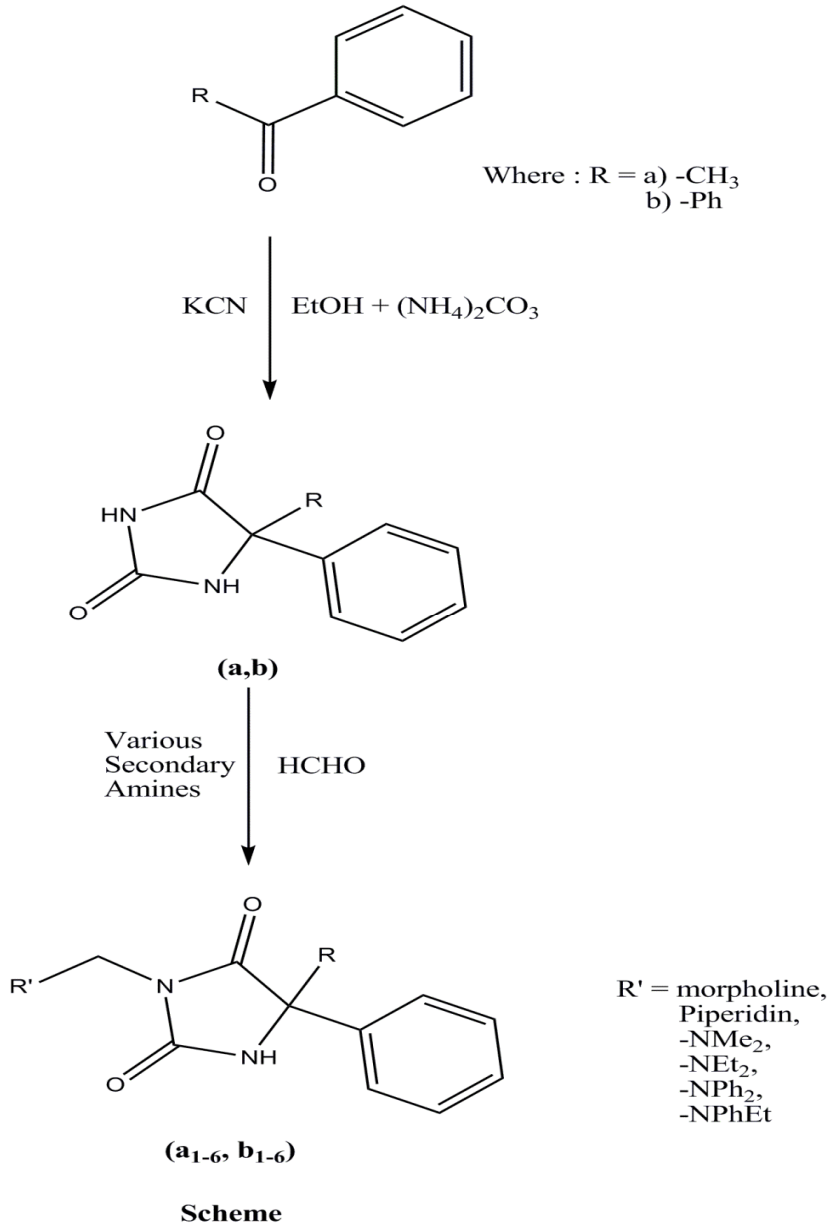
3-alkyl-5-methyl-5-phenylimidazolidine-2,4-dione (a1-6, b1-6)
Compound **a** (2gm, 0.01mol) / **b** (2.52gm, 0.01mol) were dissolved in ethanol as per required quantity then formaldehyde (0.45gm, 0.015mol) was added with steady stirring. After compellation of addition various Secondary Amines. (0.01mole) were added and then few drops of hydrochloric acid was added as catalyst and whole reaction mixture was refluxed for 6-7 hr, entire reaction was governed by TLC. After completion of reaction, mixture was made acidic (pH, 3-4) by adding hydrochloric acid then solvent was evaporating to get off white product. Which was purified by column chromatography and recrytalize from methanol.

(a1) 5-methyl-3-(morpholinomethyl)-5-phenylimidazolidine-2,4-dione
mp 158°C ; yield 70 %; FTIR (KBr/cm^{-1}) : 1517 (C=C, Ar), 1716 (C=O, amide), 2830,1460 (C-N), 1355, 1300 (C-O-C), 2900, 2950 (C-H, aliphatic), 3110 (C-H, Ar), 3250 (NH, amide); ^{1}H NMR (DMSO, δ): 1.73 (s, 3H, -CH_3), 2.10 (s, 4H, -CH_2N, Morpholine), 3.3 (brs, 4H, -CH_2O, Morpholine), 5.05 (s, 2H, -CH_2-exocyclic), 7.25-7.52 (m, 5H, Ar-H), 8.32 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 25.6, 52.8, 64.1, 66.4, 69.3, 127.6, 129.2, 129.6, 140.7, 156.6, 175.5, Elemental analysis: $C_{15}H_{19}N_3O_3$; Found (C, 62.22; H, 6.58; N, 14.55; O,16.55%); requires (C, 62.27; H, 6.62; N, 14.52; O, 16.59,%); m/z: 289.17 (M+).

(a2) 5-methyl-5-phenyl-3-(piperidin-1-ylmethyl)imidazolidine-2,4-dione
mp 185°C; yield 74 %; FTIR (KBr/cm^{-1}) : 1524 (C=C, Ar), 1711 (C=O, amide), 2918, 2965 (C-H, aliphatic), 3102 (C-H, Ar), 3262 (NH, amide); ^{1}H NMR (DMSO, δ): 1.51 (m, 6H, piperidine), 1.71 (s, 3H, -CH_3), 2.78 (t, 4H, piperidine), 5.07 (s, 2H, -CH_2-exocyclic), 7.18-7.59 (m, 5H, Ar-H), 8.34 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 24.5, 25.6, 53.8, 64.1, 69.3, 127.6, 129.2, 129.6, 140.7, 156.6, 175.5, Elemental analysis: $C_{16}H_{21}N_3O_2$; Found (C, 66.84; H, 7.32; N, 14.69; O, 11.12%); Requires (C, 66.88; H, 7.37; N, 14.62; O, 11.14,%); m/z: 287.18 (M+).

(a3) 3-((dimethylamino)methyl)-5-methyl-5-phenylimidazolidine-2,4-dione
mp 191°C ; yield 77 %; FTIR (KBr/cm^{-1}) : 1520 (C=C, Ar), 1724 (C=O, amide), 2911, 2962 (C-H, aliphatic), 3114 (C-H, Ar), 3260 (NH, amide); ^{1}H NMR (DMSO, δ): 1.73 (s, 3H, -CH_3), 2.49 (s, 6H,), 5.05 (s, 2H, -CH_2-exocyclic), 7.215-7.61 (m, 5H, Ar-H), 8.29 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 25.6, 43.7, 68.8, 69.3, 127.6, 129.2, 129.6,

140.7, 156.6, 175.5, Elemental analysis: $C_{13}H_{17}N_3O_2$; Found (C, 63.18; H, 6.92; N, 16.95; O, 12.95%); Requires (C, 63.14; H, 6.93; N, 16.99; O, 12.94,%); m/z: 247.13 (M+).



(a_{1-6}, b_{1-6})

Scheme

(a4) 3-((diethylamino)methyl)-5-methyl-5-phenylimidazolidine-2,4-dione
mp 182° ; yield 69 %; FTIR (KBr/cm-1) : 1515 (C=C, Ar), 1728 (C=O, amide), 2913, 2957 (C-H, aliphatic), 3110 (C-H, Ar), 3252 (NH, amide); ^{1}H NMR (DMSO, δ): 1.03 (t, 6H, ethyl), 1.77 (s, 3H, -CH_3), 2.85 (q, 4H, Ethyl), 5.05 (s, 2H, -CH_2-exocyclic), 7.20-7.52 (m, 5H, Ar-H), 8.30 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 13.0, 25.6, 47.0, 69.3, 127.6, 129.2, 129.6, 140.7, 156.6, 175.5, Elemental analysis: $C_{15}H_{21}N_3O_2$; Found (C, 65.45; H, 7.65; N, 15.22; O, 11.61%); Requires (C, 65.43; H, 7.69; N, 15.26; O, 11.62%); m/z: 275.16 (M+).

(a5) 3-((diphenylamino)methyl)-5-methyl-5-phenylimidazolidine-2,4-dione
mp 180°C ; yield 63% ; FTIR (KBr/cm-1) : 1065, 1080 (C-Cl), 1510 (C=C, Ar), 1710 (C=O, amide), 2910, 2952 (C-H, aliphatic), 3119 (C-H, Ar), 3246 (NH, amide); ^{1}H NMR (DMSO, δ): 1.69 (s, 3H, -CH_3), 5.06 (s, 2H, -CH_2-exocyclic), 6.92-7.81 (m, 15H, Ar-H), 8.35 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 25.6, 69.3, 73.8, 119.1, 121.9,

127.6, 129.2, 129.6, 140.7, 149.1, 156.6, 175.5, Elemental analysis: $C_{23}H_{21}N_3O_2$; Found (C, 74.38; H, 5.67; N, 11.35; O, 8.64%); Requires (C, 74.37; H, 5.70; N, 11.31; O, 8.61%); m/z: 371.16 (M+).

(a6) 3-((ethyl(phenyl)amino)methyl)-5-methyl-5-phenylimidazolidine-2,4-dione
mp 195°C ; yield 60% ;S FTIR (KBr/cm-1) : 1060, 1083 (C-Cl), 1520 (C=C, Ar), 1719 (C=O, amide), 2916, 2961 (C-H, aliphatic), 3121 (C-H, Ar), 3251 (NH, amide); ^{1}H NMR (DMSO, δ): 1.03(t, 3H, C_2H_5), 1.73 (s, 3H, -CH_3), 2.89 (q, 2H, C_2H_5), 5.08 (s, 2H, -CH_2-exocyclic), 7.19-7.89 (m, 8H, Ar-H), 8.32 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 12.6, 25.6, 44.1, 69.3, 71.4, 114.3, 121.9, 127.6, 129.2, 129.6, 140.7, 149.1, 156.6, 175.5, Elemental analysis: $C_{19}H_{21}N_3O_2$; Found (C, 70.52; H, 6.54; N, 12.95; O, 9.86%); Requires (C, 70.57; H, 6.55; N, 12.99; O, 9.89%); m/z: 323.16 (M+).

(b1) 3-(morpholinomethyl)-5,5-diphenylimidazolidine-2,4-dione
mp 199°C ; yield 73%; FTIR (KBr/cm^{-1}) : 1516 (C=C, Ar), 1720 (C=O, amide), 2833,1461 (C-N), 1356, 1299 (C-O-C) 2903, 2951 (C-H, aliphatic), 3112 (C-H, Ar), 3250 (NH, amide), ^{1}H NMR (DMSO, δ): 1.62 (s, 3H, -CH_3), 2.12 (s, 4H, -CH_2N, Morpholine), 3.5 (brs, 4H, -CH_2O, Morpholine) , 5.06 (s, 2H, -CH_2-exocyclic), 7.11-7.84 (m, 10H, Ar-H), 8.31 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 52.8, 64.1, 66.4, 73.7, 126.2, 128.2, 129.2, 139.8, 156.6, 161.9, Elemental analysis: $C_{20}H_{21}N_3O_3$, Found (C, 68.32; H, 6.05; N, 11.98; O, 13.65 %); Requires (C, 68.36; H, 6.02; N, 11.96; O, 13.66 %); m/z: 351.16 (M+).

(b2) 5,5-diphenyl-3-(piperidin-1-ylmethyl)imidazolidine-2,4-dione
mp 203°C ; yield 64%; FTIR (KBr/cm-1) : 1517 (C=C, Ar), 1716 (C=O, amide), 2905, 2951 (C-H, aliphatic), 3115 (C-H, Ar), 3254 (NH, amide); ^{1}H NMR (DMSO, δ): 1.52 (m, 6H, pireridine), 2.75 (t, 4H, piperidine), 5.06 (s, 2H, -CH_2-exocyclic), 7.17-7.88 (m, 10H, Ar-H), 8.33 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 24.5, 25.6, 53.8, 64.1, 73.7, 126.2, 128.2, 129.2, 139.8, 156.6, 161.9, Elemental analysis: $C_{21}H_{23}N_3O_2$; Found (C, 72.16; H, 6.65; N, 12.04; O, 9.13 %); Requires (C, 72.18; H, 6.63; N, 12.03; O, 9.16 %); m/z: 349.18 (M+).

(b3) 3-((dimethylamino)methyl)-5,5-diphenylimidazolidine-2,4-dione
mp 189°C ; yield 59%; FTIR (KBr/cm^{-1}) : 1512 (C=C, Ar), 1715 (C=O, amide), 2915, 2963 (C-H, aliphatic), 3119 (C-H, Ar), 3250 (NH, amide), ^{1}H NMR (DMSO, δ): 2.51 (s, 6H), 5.02 (s, 2H, -CH_2-exocyclic), 7.05-7.87 (m, 10H, Ar-H), 8.35 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 43.7, 68.8, 73.7, 126.2, 128.2, 129.2, 139.8, 156.6, 161.9, Elemental analysis: $C_{18}H_{19}N_3O_2$; Found (C, 69.89; H, 6.15; N, 13.55; O, 10.37 %); Requires (C, 69.88; H, 6.19; N, 13.58; O, 10.34 %); m/z: 309.15 (M+).

(b4) 3-((diethylamino)methyl)-5,5-diphenylimidazolidine-2,4-dione
mp 149°C; yield 68%; FTIR (KBr/cm^{-1}) : 1517 (C=C, Ar), 1721 (C=O, amide), 2901, 2947 (C-H, aliphatic), 3112 (C-H, Ar), 3247 (NH, amide), ^{1}H NMR (DMSO, δ): 1.01(t,6H, ethyl), 2.83 (q, 4H, ethyl), 5.05 (s, 2H, -CH_2-exocyclic), 7.09-7.82 (m, 10H, Ar-H), 8.36 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 13.0, 47.0, 63.8, 73.7, 126.2, 128.2, 129.2, 139.2, 156.6, 161.9, Elemental analysis: $C_{20}H_{23}N_3O_2$; Found (C, 71.16; H, 6.84; N, 12.44; O, 9.51 %); Requires (C, 71.19; H, 6.87; N, 12.45; O, 9.48 %); m/z: 337.18 (M+).

(b5) 3-((diphenylamino)methyl)-5,5-diphenylimidazolidine-2,4-dione
mp 147°C; yield 63%; FTIR (KBr/cm^{-1}) : 1062, 1088 (C-Cl), 1518 (C=C, Ar), 1720 (C=O, amide), 2921, 2964 (C-H, aliphatic), 3116 (C-H, Ar), 3250 (NH, amide), ^{1}H NMR (DMSO, δ): 5.08 (s, 2H, -CH_2-exocyclic), 6.85-7.84 (m, 10H, Ar-H), 8.31 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 73.7, 73.8, 119.1, 121.9, 126.2, 129.2, 129.6, 139.2, 149.1, 156.6, 161.9, Elemental analysis: $C_{28}H_{23}N_3O_2$; Found (C, 77.60; H, 5.37; N, 9.65; O, 7.40 %); Requires (C, 77.58; H, 5.35; N, 9.69; O, 7.38 %); m/z: 433.18 (M+).

(b6) 3-((ethyl(phenyl)amino)methyl)-5,5-diphenylimidazolidine-2,4-dione
mp 210°C; yield 71%; FTIR (KBr/cm^{-1}) : 1072, 1081 (C-Cl), 1521 (C=C, Ar), 1724 (C=O, amide), 2910, 2955 (C-H, aliphatic), 3110 (C-H, Ar), 3258 (NH, amide), ^{1}H NMR (DMSO, δ):1.02 (t, 3H, C_2H_5), 2.85 (q, 2H, C_2H_5), 5.03 (s, 2H, -CH_2-exocyclic), 6.91-7.80(m, 15H, Ar-H), 8.33 (brs, 1H, NH); ^{13}C NMR (DMSO, δ): 12.6, 44.1, 71.4, 73.7, 114.3, 121.9, 126.2, 128.2, 129.2, 129.6, 139.2, 156.6, 161.9, Elemental analysis: $C_{24}H_{23}N_3O_2$; Found (C, 74.75; H, 6.04; N, 10.92; O, 8.29 %); Requires (C, 74.78; H, 6.01; N, 10.90; O, 8.30 %); m/z: 385.18 (M+).

Antimicrobial Activity
All the synthesized compounds were tested in concentrations of 0.1 g/ml using dimethylformamide (DMF) as a solvent. The microorganisms used were as follows: Gram-negative bacteria, *E. coli*, *P. aeruginosa*; Gram-positive bacteria, *B. subtilis*, *S. aureus*, and Fungi, *P. piricola*, *F. oxysporum*.

Medium:
The cap-assay method containing (g/l) peptone (6.0), yeast extract (3.0), meat extract (1.5), glucose (1.0), and agar (20.0) were used. The medium was sterilized and divided while hot

(50-60 ºC) into 15-ml portions among sterile Petri dishes 9 cm in diameter. One ml of the spore suspension of each microorganism was spread all over the surface of the cold solid medium placed in the Petri dish.

Method:
Portions of 0.5 g of each tested compound were dissolved in 5ml of DMF. An amount of 0.1ml of the test solution was placed on Whatman paper dish, 9 mm in diameter, and the solvent was left to evaporate. These saturated discs were placed carefully on the surface of the inoculated solid medium; each Petri dish contained at least three dishes. The Petri dishes were incubated at 5 ºC for an hour to permit good diffusion, then transferred to an incubator at 85 ºC overnight, and then examined. The results were recorded by measuring the inhibition zone diameters and are presented in Table 1.

Table-1. Antimicrobial activities of the tested compounds

Tested compounds and standards	Inhibition zone (mm)					
	Gram-negative bacteria		Gram-positive bacteria		Fungi	
	E. coli.	*P.aeruginosa*	*B. subtilis*	*S. aureus*	*P.piricola*	*F. oxysporum*
Penicillin	16	15	22	17	-	-
Nystalin	-	-	-	-	24	18
a1	14	13	20	19	21	15
a2	12	12	18	15	19	13
a5	11	10	21	10	14	09
a6	11	11	13	09	13	10
b1	17	15	23	15	23	19
b2	14	13	20	16	20	18
b5	16	14	18	12	17	16
b6	11	10	16	15	15	14

RESULTS AND DISCUSSION

Chemistry
In the present communication, a novel series 3,5-substituted imidazolidine-2,4-dione were prepared via Mannich reaction between secondary amines and hydantoin derivatives by facile and fast procedure. All the newly synthesized compounds were characterized by IR, NMR, MS sprectra and elemental analyses and also screened for their antimicrobial studies. Their results revealed that the present work provided a novel class of 3,5-substituted imidazolidine-2,4-dione derivatives with potent microbial activities for further optimization.

Characterization of the synthesized compounds
The structures of the resulting compounds were established by elemental analysis, IR, NMR and MS spectral data. The proposed structure given to 3,5-substituted imidazolidine-2,4-dione derivatives were support by IR analysis which showed band at 1716 cm^{-1} (amide, CO) and 3250 cm^{-1} (amide, NH). Its ^{1}H NMR spectrum revealed signals at δ 5.07 ppm (-CH_2 exocyclic) and δ 8.34 ppm (NH) attributed to imidazolidine-2,4-dione ring protons and multiplate at δ 7.18 to 7.80 ppm corresponding to aromatic protons. Furthermore, the mass spectra gave a molecular ion peak at expectation values. The structures of all these compounds were confirmed from their correct spectral data (cf. the Experimental section).

Antimicrobial studies
All the newly synthesized compounds were screened for their antibacterial and antifungal activity. For antibacterial studies microorganisms employed were *P.aeruginosa, Escherichia coil, B. subtilis and S. aureus*. For antifungal, *P. piricola and F. oxysporum* were used as microorganisms. Both antimicrobial studies were assessed by inhibition

zone (mm). The data are summarized in Table I and show that all compounds display certain activity against the tested microorganisms.

From SAR we can see that the antibacterial and antifungal activity of the synthesized compounds may be due the presence of the versatile pharmacophore which might increase the lipophilic character of the molecules, which facilitate the crossing through the biological membrane of the microorganism and thereby inhibit their growth.

CONCLUSION

The preparation procedure follow in this work for synthesis of the title compounds offers reduction in the reaction time, operation simplicity, cleaner reaction, easy work-up and improved yields. All spectroscopic analysis confirmed the proposed structures of these compounds. Biological activity data have shown that the synthesized compounds have a significant biological activity against the tested microorganisms.

In conclusion, a series of novel 3,5-substituted imidazolidine-2,4-dione derivatives have been synthesized and evaluated for their antibacterial activity and antifungal activity against various bacteria and fungi. Many of the synthesized compounds showed good activity against the test bacteria and fungi.

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