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Synthesis and antimicrobial evaluation of bis imidazolidinone assembled dihydropyridine ethoxyphthalimide derivatives

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Abstract: In the present investigation there is an easy access to a series of imidazole containing dihydropyridine attached alkoxyphthalimide moiety in a single molecule. Schiff bases **(3a-c)** of the compound 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbohydrazide **(2)** was prepared by refluxing it with substituted benzaldehydes which in turn was obtained by condensation of benzaldehyde with ethylaectoacetate followed by treatment of hydrazine hydrate. Condensation of **(3a-c)** with bromoethoxyphthalimide yielded compound **(4a-c)**. Further cyclization of **(4a-c)** to the multinucleated final compound **(5a-c)** was achieved by treating this with glycine in a mixed solvent. Structure of compounds was confirmed by analytical, spectral data & chemical tests. Six of these compounds have been screened for antimicrobial screening against 4 bacterial and 2 fungal pathogenic strains. Half of the compounds showed appreciable activity.

Keywords: Bromoethoxyphthalimide, Ethylaectoacetate, Benzaldehyde, Dihydropyridine, Antimicrobial.

Introduction

1,4 Dihydropyridines are important class of compounds in the field of drugs and pharmaceuticals. Researches on Dihydropyridine and its synthetic analogs has revealed that they possess many biological activities such as, vasodilates [1], antihypertensive [2], anti-inflammatory [3], anti-ischemic agents [4], calcium channel modulators of the nifedipne type [5], bronchodilatory and antitubercular [6-8], antianginal [9-11], antitumor [12], antithrombotic [13], analgesic [14], anticonvulsant [15], antimicrobial [16], stress protective effect [17] and cardio depressant activity [18] etc. A perusal of the literature has revealed manifold potential pharmaceutical implications of imdazole and its derivatives viz. immunosuppressive agents [19], rediosensitizer and bioreductively activated cytotoxins [20], antiedema and anti-inflammatory [21], antimicrobial [22], antiviral [23], anti-cancer [24] and COX-2/LOX inhibitor [25], melanocortin-4 receptor (MC4-R) antagonists [26], antitubercular [27]. As reported, imidazole rings are widely employed as spin-trapping species in the interesting application of designing drugs with neuroprotective activity [28]. In view of strong pharmacophic properties of alkoxyphthalimide moiety several derivatives of alkoxyphthalimide have been synthesized [29] and reported to demonstrate a wide range of pharmacological activities i. e. anticancer [30], antimalarial [31], anticonvulsant [32], diuretic [33] etc. Based on above observation, synthesis of some new imidazole, 1,4-dihydropyridine and phthalimidoxy containing molecules have been prepared and evaluated for antimicrobial activity.
Statistical relationship of synthesized molecules has been correlated with different drug molecules.

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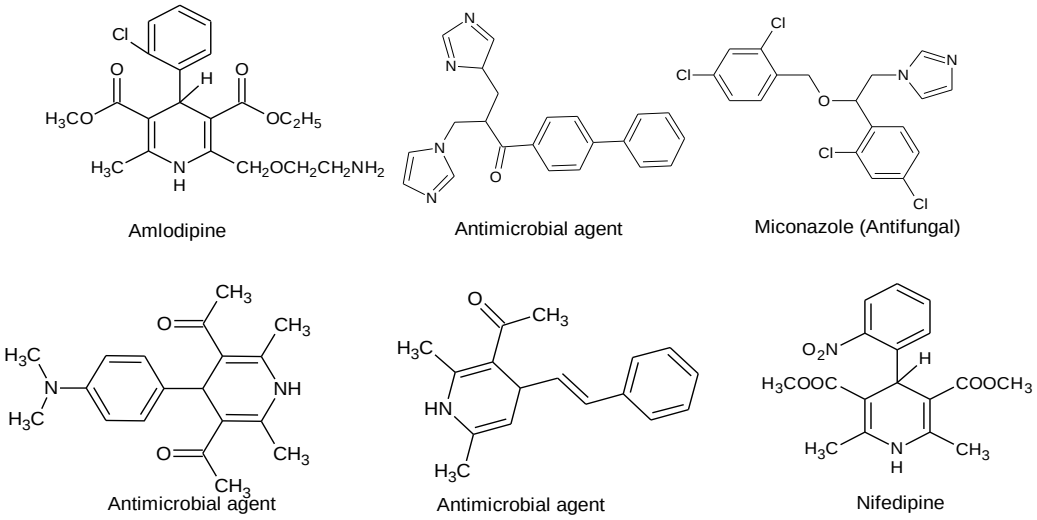


Figure 1: Some examples of Heterocycles containing imidazole and dihydropyridine moieties.

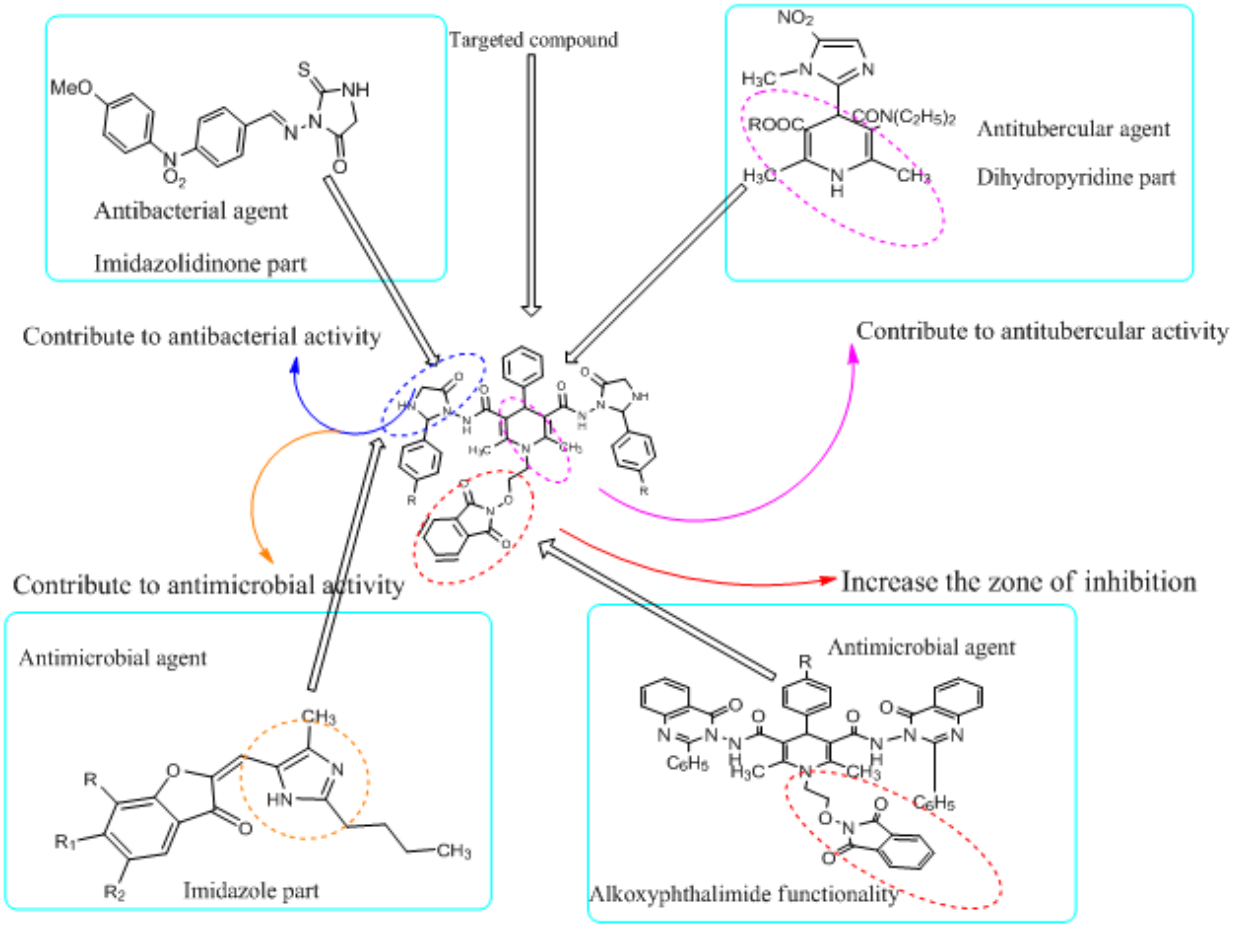
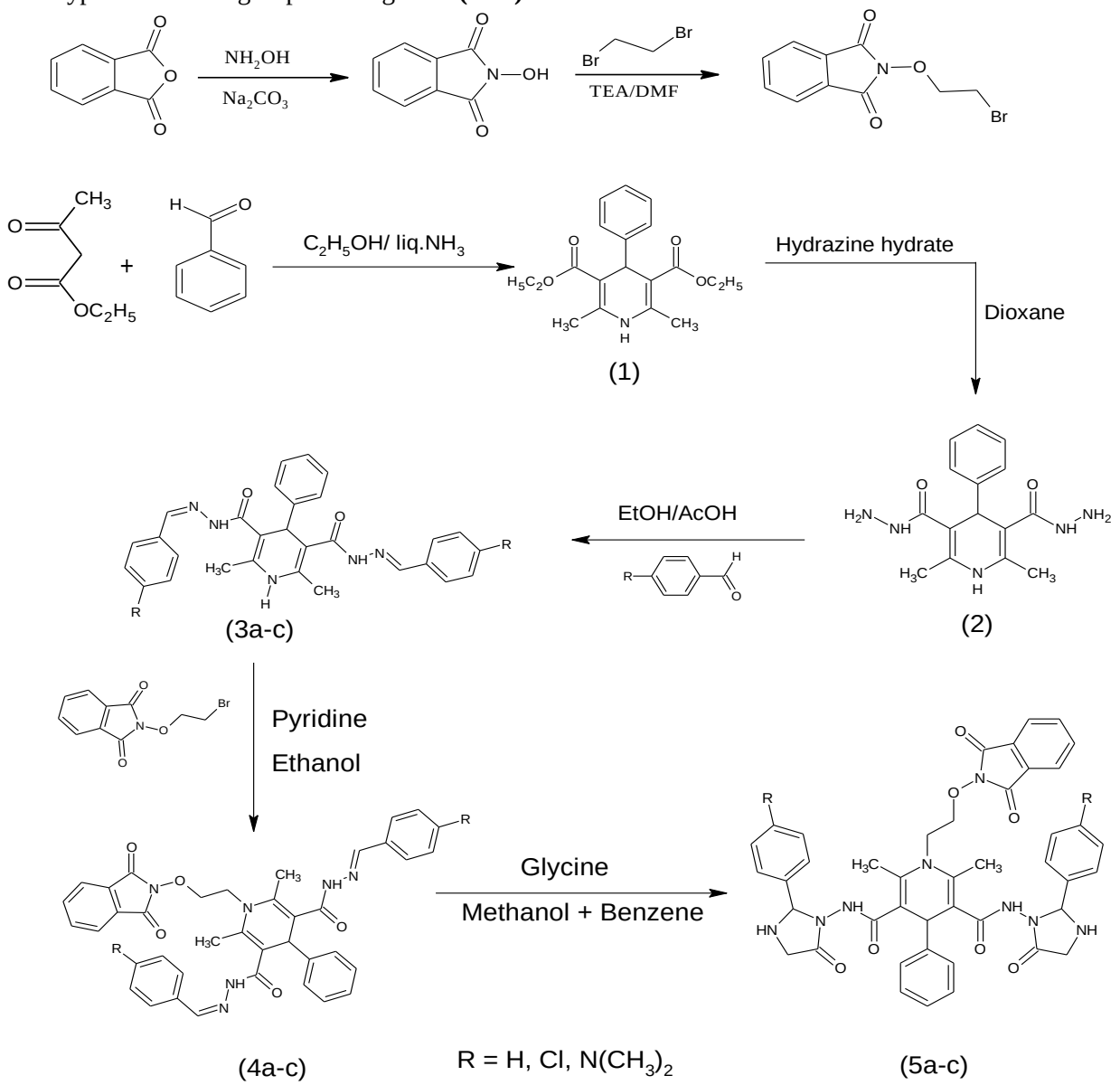


Figure 2: Statistical relationship of synthesized molecules has been correlated with different drug molecules

Results and discussion

The synthetic route for obtaining final compounds is presented in scheme **1**. Physical and analytical data have given in Table **1**. The cyclocondensation of three compounds Viz. ethylaectoacetate, benzaldehyde and ammonia yielded compound **(1)**. The structure of the compound was assigned on the basis of spectral data:

3307 cm^{-1} for –NH in IR and triplet at δ = 1.4, quartet = 3.7 in ^1H NMR. Compound **(2)** was obtained from **(1)** and hydrazine hydrate via condensation reaction. Disappearance of triplet at δ = 1.4, quartet = 3.7 in ^1H NMR and appearance of new triplet at δ = 8.2 for NH proton in ^1H NMR confirmed the structure of compound **(2)**. Compound (**2)** was further converted into their corresponding Schiff base derivatives **(3a-c)** by reaction with substituted aldehydes. Formation of the product was confirmed by the presence of new singlet at δ = 8.9 for CH proton of -N=CH and a strong band at 1572 cm^{-1} for C=N group in IR. Subsequently, the H atom of N-H was replaced by the bromoethoxyphthalimide group to give **(4a-c)**. Stretching at 1315 cm^{-1} for N-O and absence of singlet at δ = 8.3 for N-H proton in ^1H NMR confirming the presence of imidoxy moiety in **(4a)**, this was further supported by ^{13}C NMR data and molecular ion peak in the mass spectrum. In order to synthesize **(5a-c)** compound **(4a-c)** were treated with glycine in (methanol + benzene) mixed solvent. Disappearance of strong C=N band at 1601 cm^{-1} which was present in its precursor and presence of singlet at δ = 8.12 for N-H proton in ^1H NMR spectrum confirmed the formation of target compound **(5a)**. Analytical and spectral data for synthesized compounds are given in experimental section.



Scheme 1: Synthesis of ethoxyphthalimide derivatives of Dihydropyridine.

Table 1: Anti bacterial and Anti fungal activity of Compounds zone of inhibition in mm (Activity index).

Compound No	Anti bacterial activity (50µg/mL)				Anti fungal activity (50µg/mL)	
	Gram +ve		Gram –ve			
	B_1	B_2	B_3	B_4	F_1	F_2
4a	15 (0.71)	16 (0.69)	18 (0.72)	16 (0.66)	14 (0.63)	17 (0.60)
4b	17 (0.80)	18 (0.78)	20 (0.80)	21 (0.87)	17 (0.77)	20 (0.71)
4c	13 (0.61)	15 (0.65)	21 (0.84)	13 (0.54)	12 (0.54)	15 (0.53)
5a	16 (0.76)	17 (0.73)	19 (0.76)	17 (0.70)	16 (0.72)	19 (0.67)
5b	19 (0.90)	20 (0.86)	22 (0.88)	20 (0.83)	18 (0.81)	23 (0.82)
5c	17 (0.80)	19 (0.82)	17 (0.68)	15 (0.62)	13 (0.59)	17 (0.60)
C_1	21	23	25	24	-	-
C_2	-		-	-	22	28

B_1 = *Staphylococcus aureus*, B_2 = *Streptococcus pyogenes*, B_3 = *Escherichia coli*,
B_4 = *Pseudomonas aeruginosa*, F_1 = *Candida albicans*, F_2 = *Aspergillus clavatus*
C_1 = Cefixime standard drug for antibacterial activity.
C_2 = Griseofulvin standard drug for Antifungal activity.

Conclusion

In the present work, a series of Dihydropyridine derivatives were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis. The compounds were screened for its antimicrobial activity. Antimicrobial results indicated that the compounds **4b** and **5b** showed significant activity towards all bacterial and fungal strains when compared to standard drugs.

Experimental

All the melting points were determined by electro thermal method in open capillary tubes and are therefore uncorrected. The IR spectra of the compounds were recorded on a 4000-450 cm^{-1} ranges using KBr discs on FTIR IR RX1Perkin Elmer spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-200 MHz spectrometer in ($CDCl_3$) solvent using TMS as an internal standard. The mass spectra were recorded on a Jeol SX-102 (FAB) mass spectrometer. Purity of the synthesized compounds was checked on silica gel G TLC plates of 2 mm thickness using suitable solvent. The visualization of spot was carried out in an iodine chamber. Bromoethoxyphthalimide was prepared by reported method [34]. Structures of all the synthesized compounds were assigned on basis of their chemical tests as well as analytical and spectral data.

Synthesis of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1):

To a solution of aromatic aldehyde (0.01mol) in ethanol (50 mL), Ethylaectoacetate (0.02 mol) and ammonia liquor (2.5 mL) were added. The reaction mixture was refluxed for 4-5 hrs and the solid obtained was collected and filtered. It was washed with ethanol and recrystallized from ethanol. Yield 66%, m.p. 157-159; IR (KBr, cm^{-1}): 3062 (Ar C-H str.), 2952 (CH_3, C-H str.), 1043 (C-O str.), 1713 (-C=O str.), 3307 (N-H str.); ^{1}H NMR ($CDCl_3$, δ): 6.83-7.62 (m, 5H, Ar-H), 8.21 (s, 1H, -NH), 2.1 (s, 6H, CH_3), 1.4 (t, 6H, CH_3), 3.7 (q, 4H, CH_2), 4.3 (s, 1H, Ar- CH); MS m/z 329 $[M]^{+\cdot}$; Anal. Calcd. For $C_{19}H_{23}NO_4$: N, 4.25. Found: N, 4.21%.

Synthesis of 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbohydrazide (2):

A mixture of **1 (**0.005 mol) and hydrazine hydrate (0.01 mol) in dioxane (25 mL) were refluxed for 8-10 hrs. The mixture was concentrated by distillation under reduced pressure. The concentrated mixture was poured over crushed ice. The solid formed was recrystallized from ethanol. Yield 64%, m.p. 132-134; IR (KBr, cm^{-1}): 3072 (Ar C-H str.), 2969 (CH_3, C-H str.), 1704 (-C=O str.), 3352 (N-H str.); ^{1}H NMR ($CDCl_3$,δ): 6.98-7.38 (m, 5H, Ar-H), 8.07 (s, 1H, -NH), 2.6 (s, 6H, CH_3), 8.2 (t, 2H, N-H), 2.8(d, 4H, NH_2), 4.9 (s, 1H, Ar- CH); MS m/z 301$[M]^{+\cdot}$; Anal. Calcd. For $C_{15}H_{19}N_5O_2$: N, 23.24. Found: N, 22.42%.

Synthesis of dibenzylidene-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbohydrazide (3a):

The compound **2** (0.005 mol) was dissolved in ethanol (50 mL), sodium acetate (0.01 mol), benzaldehyde (1.1 mL) and two drops of conc. sulphuric acid was added and the reaction mixture was heated under reflux for 16-18 hrs. The excess of solvent was distilled-off under reduced pressure. The residue so obtained was washed with dry ether and recrystallized from methanol. Yield 82%, m.p. 147-150; IR (KBr, cm^{-1}): 3075 (Ar C-H str.), 2957 (CH_3, C-H str.), 1572 (C=N str.), 1709 (-C=O str.), 3334 (N-H str.); ^{1}H NMR ($CDCl_3$, δ): 7.12-7.80 (m, 15H, Ar-H), 8.09 (s, 1H, -NH), 2.3 (s, 6H, CH_3), 8.5 (s, 2H, NH), 8.91 (s, 2H, CH), 4.4 (s, 1H, Ar- CH); MS m/z 477 $[M]^{+\cdot}$; Anal. Calcd. For $C_{29}H_{27}N_5O_2$: N, 14.66. Found: N, 13.67%.

Similarly, all the compounds **(3b-c)** were synthesized by using above method with minor change in reaction conditions.

bis(4-chlorobenzylidene-2,6-dimethl-4-phenyl-1,4-dihydropyridine-3,5-dicarbohydrazide (3b):

Yield 85%, m.p. 163-165; IR (KBr, cm^{-1}): 3075 (Ar C-H str.), 2965 (CH_3, C-H str.), 1610 (C=N str.), 1718 (-C=O str.), 3358 (N-H str.), 752 (C-Cl); ^{1}H NMR ($CDCl_3$, δ): 7.34-7.98 (m, 13H, Ar-H), 8.29 (s, 1H, -NH), 2.7 (s, 6H, CH_3), 8.87 (s, 2H, NH), 9.01 (s, 2H, CH), 4.76 (s, 1H, Ar- CH); MS m/z 545 $[M]^{+\cdot}$, 547 $[M+2]^{+\cdot}$, 549 $[M+4]^{+\cdot}$; Anal. Calcd. For $C_{29}H_{25}Cl_2N_5O_2$: N, 12.82. Found: N, 11.56%.

bis(4-(dimethylamino)benzylidene-2,6-dimethyl-4-phenyl-1,4dihydropyridine-3,5 dicarbohydrazide (3c):

Yield 74%, m.p. 144-146; IR (KBr, cm^{-1}): 3056 (Ar C-H str.), 2948 (CH_3, C-H str.), 1558 (C=N str.), 1700 (-C=O str.), 3323 (N-H str.); ^{1}H NMR ($CDCl_3$, δ): 6.93-7.37 (m, 13H, Ar-H), 7.89 (s, 1H, -NH), 1.78 (s, 6H, CH_3), 8.1 (s, 2H, NH), 8.31 (s, 2H, CH), 4.1(s, 1H, Ar-CH), 2.89 (s, 12H, $N(CH_3)_2$); MS m/z 563 $[M]^{+\cdot}$; Anal. Calcd. For $C_{33}H_{37}N_7O_2$: N, 17.39. Found: N, 15.38%.

Synthesis of dibenzylidene-1-(2-(1,3-dioxoisoindolin-2-yloxy)ethyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine -3,5-dicarbohydrazide (4a):

A mixture of **3** (0.005 mol) and bromoethoxyphthalimide (0.005 mol) in absolute ethanol (15 mL) was refluxed for 16-18 hrs using pyridine (0.01 mol) as a base. It was concentrated by removing the solvent under reduced pressure and the resultant filtrate was poured into crushed ice to obtain solid product, which was filtered, dried and recrystallized from alcohol. Yield 59%, m.p. 130-132; IR (KBr, cm^{-1}): 3070 (Ar C-H str.), 2963 (CH_3, C-H str.), 1601 (C=N str.), 1048 (C-O str.), 1716 (-C=O str.), 1315 (N-O str.); ^{1}H NMR ($CDCl_3$, δ): 7.88-7.13 (m, 19H, Ar-H), 2.3 (s, 6H, CH_3), 8.3 (s, 2H, NH), 8.8 (s, 2H, CH), 4.6 (s, 1H, Ar- CH), 3.5 (t, 2H, OCH_2), 3.1 (t, 2H, NCH_2);^{13}C NMR (50 MHz, $CDCl_3$ δ): 166.98, 162.34, 147.09, 145.23, 143.20, 137.89, 136.45, 131.43, 129.03, 127.34, 127.16, 125.43, 103.48, 77.00, 76.37, 75.73, 59.06, 38.95, 18.92, 13.58; MS m/z 666 $[M]^{+\cdot}$; Anal. Calcd. For $C_{39}H_{34}N_6O_5$: N, 12.60. Found: N, 10.89%.

Similarly, all the compounds **(4b-c)** were synthesized by the above method with minor change in reaction conditions.

bis(4-chlorobenzylidene-1-(2-(1,3-dioxoisoindolin-2-yloxy)ethyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine -3,5-dicarbohydrazide (4b):

Yield 63%, m.p. 139-141; IR (KBr, cm^{-1}): 3079 (Ar C-H str.), 2974 (CH_3, C-H str.), 1612 (C=N str.), 1055 (C-O str.), 1723 (-C=O str.), 1324 (N-O str.), 768 (C-Cl); ^{1}H NMR ($CDCl_3$, δ): 8.18-7.76 (m, 17H, Ar-H),

2.5 (s, 6H, CH_3), 8.7 (s, 2H, NH), 9.2 (s, 2H, CH), 4.8 (s, 1H, Ar- CH), 3.8 (t, 2H, OCH_2), 3.3 (t, 2H, NCH_2);^{13}C NMR (50 MHz, $CDCl_3$ δ); 170.89, 165.54, 149.92, 147.23, 146.58, 145.61, 142.67, 139.32, 132.12, 130.38, 129.76, 128.52, 109.71, 89.31, 83.21, 80.11, 65.00, 42.26, 20.69, 18.32; MS m/z 734 $[M]^{+\cdot}$, 736 $[M+2]^{+\cdot}$, 738 $[M+4]^{+\cdot}$; Anal. Calcd. For $C_{39}H_{32}Cl_2N_6O_5$: N, 11.42. Found: N, 9.78%.

bis(4-(dimethylamino)benzylidene-1-(2-(1,3-dioxo isoindolin-2yloxy)ethyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbohydrazide (4c):

Yield 54%, m.p. 128-133; IR (KBr, cm^{-1}): 3053 (Ar C-H str.), 2955 (CH_3, C-H str.), 1595 (C=N str.), 1034 (C-O str.), 1720 (-C=O str.), 1303 (N-O str.); ^{1}H NMR ($CDCl_3$, δ): 7.88-7.13 (m, 17H, Ar-H), 2.3 (s, 6H, CH_3), 8.3 (s, 2H, NH), 8.8 (s, 2H, CH), 4.6 (s, 1H, Ar-CH), 3.5 (t, 2H, OCH_2), 3.1 (t, 2H, NCH_2);^{13}C NMR (50 MHz, $CDCl_3$ δ); 168.11, 163.57, 146.28, 144.83, 142.10, 134.29, 131.12, 128.45, 126.39, 124.87, 123.16, 123.03, 101.18, 84.35, 76.30, 73.15, 69.33, 55.21, 39.35, 17.68, 13.98; MS m/z 752 $[M]^{+\cdot}$; Anal. Calcd. For $C_{43}H_{44}N_8O_5$: N, 14.88. Found: N, 13.35%.

Synthesis of 1-(2-(1,3-dioxoisoindolin-2-yloxy)ethyl)-2,6-dimethyl-bis(5-oxo-2-phenylimidazolidin-1-yl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboximide (5a):

Schiff's base **4** (0.005 mol) was dissolved in a mixture of dry benzene and methanol (1:1, 30 mL), glycine (0.005 mol) was added with constant stirring. This mixture was refluxed for 8-10 hrs. Solid separated was filtered and recrystallized from ethanol. Yield 52%, m.p. 99-102; IR (KBr, cm^{-1}): 3074 (Ar C-H str.), 2943 (CH_3, C-H str.), 1222 (C-N str.), 1051 (C-O str.), 1721 (-C=O str.), 1323 (N-O str.); ^{1}H NMR ($CDCl_3$, δ): 7.10-7.89 (m, 19H, Ar-H), 2.3 (s,6H, CH_3), 8.12 (s, 2H, NH), 5.90 (s, 2H, CH), 4.9 (s, 1H, Ar- CH), 3.8 (t, 2H, OCH_2), 3.4 (t, 2H, NCH_2), 3.67 (d, 4H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$ δ`); 172.12, 167.59, 154.38, 143.75, 137.43, 131.18, 129.31, 127.99, 127.81, 126.07, 104.20, 79.41, 77.63, 77.00, 76.36, 59.70, 56.49, 47.33, 39.60, 19.61, 14.22; MS m/z 780 $[M]^{+\cdot}$; Anal. Calcd. For $C_{43}H_{40}N_8O_7$: N, 14.35. Found: N, 12.67%.

Similarly, all the compounds **(5b-c)** were synthesized by the above method with minor change in reaction conditions.

bis(2-(4-chlorophenyl)-5-oxoimidazolidin-1-yl)-1-(2-(1,3-dioxoisoindolin-2-yloxy)ethyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboximide (5b):

Yield 69%, m.p. 110-112; IR (KBr, cm^{-1}): 3079 (Ar C-H str.), 2956 (CH_3, C-H str.), 1229 (C-N str.), 1059 (C-O str.), 1728 (-C=O str.), 1332 (N-O str.), 775 (C-Cl); ^{1}H NMR ($CDCl_3$, δ): 7.67-8.29 (m, 17H, Ar-H), 2.8 (s,6H, CH_3), 8.45 (s, 2H, NH), 6.20 (s, 2H, CH), 4.8 (s, 1H, Ar- CH), 3.6 (t, 2H, OCH_2), 3.2 (t, 2H, NCH_2), 3.9 (d, 4H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$ δ); 176.10, 169.38, 158.31, 146.28, 147.98, 142.65, 137.45, 132.83, 130.23, 129.10, 128.39, 108.02, 84.26, 81.62, 79.73, 64.49, 58.24, 53.23, 40.42, 21.22, 18.34; MS m/z 848 $[M]^{+\cdot}$, 850 $[M+2]^{+\cdot}$, 852 $[M+4]^{+\cdot}$; Anal. Calcd. For $C_{43}H_{38}Cl_2N_8O_7$: N, 13.19. Found: N, 11.59%.

bis(2-(4-dimethylamino)phenyl)-5-oxoimidazolidin-1-yl)-1-(2-(1,3-dioxoisoindolin-2-yloxy)ethyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboximide (5c):

Yield 65%, m.p. 121-123; IR (KBr, cm^{-1}): 3068 (Ar C-H str.), 2934 (CH_3, C-H str.), 1213 (C-N str.), 1047 (C-O str.), 1717 (-C=O str.), 1314 (N-O str.); ^{1}H NMR ($CDCl_3$, δ): 6.32-7.57 (m, 17H, Ar-H), 1.68 (s, 6H, CH_3), 8.02 (s, 2H, NH), 5.56 (s, 2H, CH), 4.1 (s, 1H, Ar- CH), 3.2 (t, 2H, OCH_2), 2.89 (t, 2H, NCH_2), 3.4 (d, 4H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$ δ`); 168.18, 164.34, 151.53, 148.97, 142.78, 134.98, 130.02, 128.13, 125.67, 125.89, 124.32, 103.48, 75.09, 72.32, 69.63, 64.89, 55.82, 51.01, 45.52, 34.44, 18.76, 13.65; MS m/z 866$[M]^{+\cdot}$; Anal. Calcd. For $C_{47}H_{50}N_{10}O_7$: N, 16.16. Found: N, 15.72%.

Antimicrobial Activity [35, 36]:

Synthesized compounds **(4a-c, 5a-c)** were screened *in vitro* for their antibacterial and antifungal activities using 50μg/mL concentration in DMSO by disc diffusion method. The micro organisms were cultured on nutrient agar/YEPD (yeast extract peptone dextrose) by using spread plate technique. The microbial strains were grown in Mueller-Hinton agar (MHA) plates at 37°C. Mueller-Hinton sterile agar plates were seeded with indicator bacterial strains (10^8 cfu) and allowed to stay at 37°C for 3 hours. Control experiments were carried out under similar condition by using a standard drug. The zones of growth inhibition around the disks were measured after 18 to 24 hrs (bacteria) 48 to 96 hrs (fungi). The measurement obtained has compared with standard to determine activity index. Antibacterial activity of compounds have been evaluated against four bacterial strains (two gram positive and two gram negative viz *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Pseudomonas aeruginosa)* using cefixime as standard. Antifungal activity of

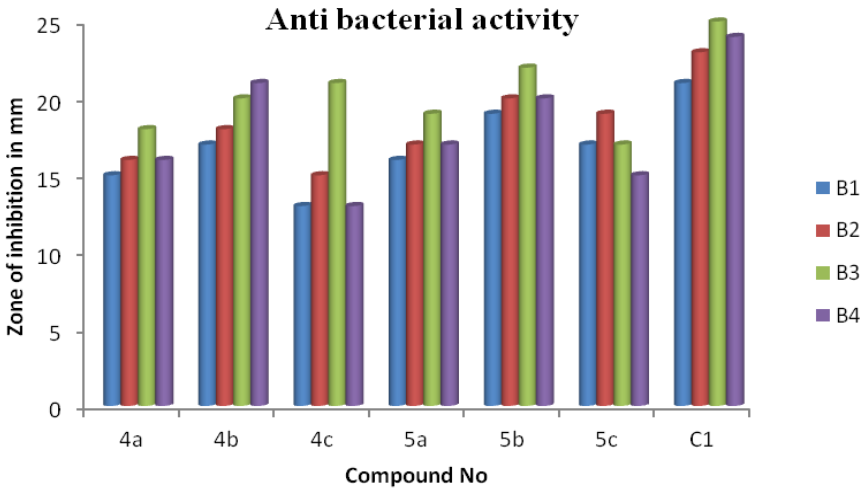
synthesized compounds was evaluated against *Candida albicans, Aspergillus clavatus* by using grisofulvin as standard drug.

Antibacterial Activity:

Results of antibacterial activity are presented on the basis of zone of inhibition and activity index (Table **1**). Out of screened compounds **4b, 5a** and **5b** shown strong activity against all bacterial strains. Compound **4c** and **5c** have shown remarkable activity against *E. coli* and *S. aureus* & *S. pyogenes.* All the rest compounds have shown good to moderate activity against all bacterial strains.

Antifungal Activity:

Compound **4b** and **5b** showed stronger activity against *Candida albicans* and *Aspergillus clavatus*. Compound **4a** and **5a** has been shown good activity against both fungal strains. Compound containing ethoxyphthalimide and imidazolidinone ring shows significant activity. Rest of the compounds possesses good to moderate activity against both fungal strains.



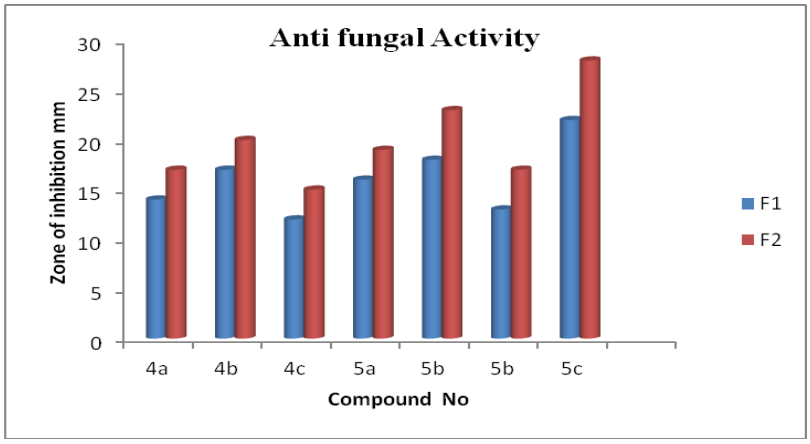


Figure 3: Comparative antimicrobial activity graphs

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