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Synthesis, characterization and pharmacological evaluation of some 1,4-dihydropyridines derivatives

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ABSTRACT

A series of 1, 4-dihydropyridine derivatives were prepared from three compounds condensation reaction of ethylacetoacetate, aromatic aldehyde and ammonium hydroxide. A new series of compounds (2a-f) were prepared from compounds (1a-f) via reaction with β-naphthayl amine using the condensation method. The synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C-NMR and Elemental analyses. The synthesized compounds (1e-f) and (2a-f) were also screened for antimicrobial properties.

Key words: Synthesis of 1, 4-Dihydropyridines and Antimicrobial activity studies

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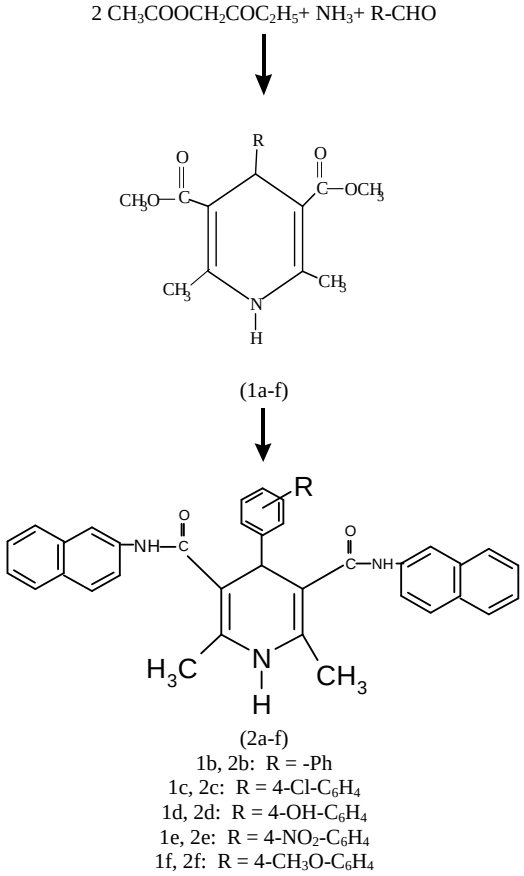
INTRODUCTION

Arthur Hantzsch first reported an efficient way to prepare the 1,4-dihydropyridine in 1882[1]. The 1,4-dihydropyridine exhibits special biological activities in the treatment of cardiovascular diseases as a calcium channel blockers. More than twelve commercial, clinically important drugs such as Amlodipine, Nifedipin, Nimodipin, Felodipine, Isradipine and Nicardipine containing the 1,4-dihydropyridine parent nucleus have been manufactured and used worldwide[2]. This 1,4-dihydropyridine nucleus is a common feature of various bioactive compounds such As a sodialator, branchiodialator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agents[3-4]. On the molecular level 1,4-dihydropyridine compounds causes vaso relaxation by blocking voltage operated calcium channel in smooth muscle cell and also by increasing no release from intact endothelium[5]. The metabolism of 1,4-dihydropyridine is catalysed by the cytochrome P450(CYP)3A4isoform[6,7].1,4-dihydropyridine are class of N containing heterocycles having a six membered ring, generated by a complex molecular system via Hantzsch (Multicomponent reaction). Almost all of the new methodologies of organic synthesis, for instance microwave assisted synthesis[8] the promotion of solar thermal energy[9] and ultrasoundradiation[10] the replacement of organic solvent by ionic liquids or water[11] the use of various metal halides or triflates as Lewis catalysts[12] have been employed for synthesis of 1,4-dihydropyridines. However most of the research has been focused on the modification and optimization of the Hantzsch reaction to maximise reaction conversion, minimise reaction time and offer high purity of 1,4-dihydropyridine compounds. Most of the existing methods for the synthesis of 1,4-dihydropyridine suffer from drawbacks such as low yield, long reaction time, occurrence of several side products, use of stoichiometric amount of reagents, strong oxidants and the expensive and toxic transition metallic reagents and catalysts.

Thus, development of an efficient and convenient synthetic methodology in aqueous medium is an important area of research. In this field, the synthesis of 1,4-dihydropyridine derivatives in aqueous media has been reported by using phase-transfer catalysts or hydro tropes under microwave irradiation or normal thermal conditions[13-17].

Reaction sequence:



1b, 2b: R = -Ph
1c, 2c: R = 4-Cl-C_6H_4
1d, 2d: R = 4-OH-C_6H_4
1e, 2e: R = 4-NO_2-C_6H_4
1f, 2f: R = 4-CH_3O-C_6H_4

EXPERIMENTAL SECTION

All chemicals were purchased from commercial suppliers. The melting points were determined on Veego-programmable melting point apparatus (microprocessor-based) and are uncorrected. 1H NMR spectra were obtained using Brucker AC-400 F, 400 MHZ spectrometer and the spectra were measured in DMSO-*d6* relative to tetramethylsilane (TMS) as internal standard and reported in parts per million (ppm). Infrared (IR) spectra were obtained with Perkin Elmer 882 Spectrum and RXI, FT-IR model using a potassium bromide pellets (in cm-1). Elemental analyses for C, H, and N were performed on Thermo-flash EA-1112 CHNS-O Analyzer.Synthesis related to microwave irradiation and ultrasonication are carried out in domestic LG little chef microwave oven and fast clean ultrasonic cleaner respectively. Reactions were monitored and the homogeneity of the products was checked by TLC which were prepared with silica gel G and activated at 110 oC for 30 min. The plates were developed by exposure to iodine vapours.All chemicals were dried and freshly prior to use according to standard procedure. All compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples.

1,4 dihydro -2,6-dimethyl - 4- (aryl substituted) pridine-3,5- dicarboxylic acid dimethyl ester (1a-f)
To a solution of aeromatic aldehyde in ethanol (0.03 mol) methyl acetoacetate (0.06mol) and liquid ammonia (5ml) were added. The mixture was refluxed for 4 hour's and the solid of tained was collected and tiltered. It was washed with cold ethanol and recrystallised from ethanol.

1,4 -di hydro-2,6- di methyl -4- aryl substituted pyridine -3,5- die - α - napthal amide (2a-f)
A mixture of 1,4 hydro-2,6- dimethyl -4- aryl substututed pyridine -3,5 dicarboxili acid dimethyl exter (I) (0.01mol) and - α-napthal amine (0.02 mol) in 1,4 dioxane (25 ml) were reflexed for 7 hour's poured crushed ice. The soiled formed is re-crystillised from methonal.

ANALYTIC AND SPECTRAL DATA
Diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1a)
Yield: 75 %; m.p.158 °C; Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39 %. Found: C, 63.98; H, 6.67; N, 4.35 %. IR (KBr, cm^{-1}): 3353 (N–H str), 3032 (Ar–H), 2940 (C–H str of CH_3), 1745 (C=O, ester), 811 (Ar–H). ^{1}H-

NMR (300 MHz, DMSO-d_6, δ / ppm): 8.34 (1H, *s*, NH of pyridine ring), 7.30 (1H, *s*, furyl ring), 6.10–6.47 (2H, *d*, furyl ring), 4.32 (1H, *s*, C4–H), 4.20 (4H, *q*, C3– –C**H**$_2$CH$_3$ and C5–OC**H**$_2$CH$_3$), 2.31 (6H, *s*, C2–CH$_3$ and C6–CH$_3$), 1.34 (6H, *t*, C2–OCH$_2$C**H**$_3$ and C6–OCH$_2$C**H**$_3$). ^{13}C-NMR (300 MHz, DMSO-d_6, δ / ppm): 142.1, 109.6, 107.7, 152.5 (furyl ring), 151.8 (C2,6), 33.2 (C4), 102.3 (3,5--**C**OOCH$_2$CH$_3$), 62.1(3,5-COO**C**H$_2$CH$_3$), 15.9 (3,5-COOCH$_2$**C**H$_3$), 18.3 (2,6--**C**H$_3$).

Diethyl2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1b)

Yield: 66 %; m.p. 253 °C; Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25 %. Found: C, 69.24; H, 7.07; N, 4.28 %. IR (KBr, cm^{-1}): 3350 (N–H str), 3034 (Ar–H), 2953 (C–H str of CH$_3$), 1755 (C=O, ester), 802 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 8.25 (1H, *s*, NH of pyridine ring), 7.33–7.27 (5H, *m*, Ph-ring), 4.70 (2H, *s*, C4–H), 4.22 (4H, *q*, C3–OC**H**$_2$CH$_3$ and C5– –OC**H**$_2$CH$_3$), 2.28 (6H, *s*, C2–CH$_3$ and C6-CH$_3$), 1.32 (6H, *t*, C2–OCH$_2$C**H**$_3$ and C6–OCH$_2$C**H**$_3$). ^{13}C-NMR (300 MHz, DMSO-d_6, δ / ppm): 125.1, 128.4, 127.1, 144.8 (phenyl ring), 150.7 (C2,6), 101.9 (3,5-**C**OOCH$_2$CH$_3$), 62.1 (3,5--COO**C**H$_2$CH$_3$), 44.1 (C4), 19.1 (2,6-**C**H$_3$), 15.4 (3,5-COOCH$_2$**C**H$_3$).

***Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbo-xylate* (1c)**

Yield: 57 %; m.p. 240 °C. Anal. Calcd. for $C_{19}H_{22}ClNO_4$: C, 62.72; H, 6.09; N, 3.85 %. Found: C, 62.75; H, 6.07; N, 3.81 %. IR (KBr, cm^{-1}): 3334 (N–H str), 3084 (Ar–H), 2944 (C–H str of CH$_3$), 1746 (C=O, ester), 832 (Ar–H), 616 (C–Cl), 787 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 8.41 (1H, *s*, NH of pyridine ring), 7.36–7.20 (5H, *m*, Ph-ring), 4.77 (1H, *s*, C4–H), 4.20 (4H, *q*, 3C–OCH$_2$CH$_3$ and C5–OCH$_2$CH$_3$), 2.19 (6H, *s*, C2–CH$_3$ and C6–CH$_3$), 1.33 (6H, *t*, C2–OCH$_2$CH$_3$ and C6–OCH$_2$CH$_3$). ^{13}C-NMR (300 MHz, DMSO-d_6, δ / / ppm): 131.4, 128.1, 130.8, 142.5 (Ph–Cl), 152.5 (C2,6), 34.7 (C4), 103.9 (3,5--**C**OOCH$_2$CH$_3$), 60.4 (3,5-COO**C**H$_2$CH$_3$), 15.5 (3,5-COOCH$_2$**C**H$_3$), 18.8 (2,6--CH$_3$)

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbo-xylate (1d)

Yield: 56 %; m.p. 240 °C; Anal. Calcd. for $C_{19}H_{23}NO_5$: C, 69.07; H, 6.71; N, 4.06 %. Found: C, 9.03; H, 6.75; N, 4.01 %. IR (KBr, cm^{-1}): 3342 (N–H str), 3027 (Ar–H), 2942 (C–H str of CH$_3$), 1712 (C=O, ester), 1445 (C–OH), 819 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 9.44 (1H, *s*, C–OH), 8.43 (1H, *s*, NH of pyridine ring), 6.34–7.67 (4H, *m*, Ph-ring), 4.67 (1H, *s*, C4–H), 4.22 (4H, *q*, C3–OC**H**$_2$CH$_3$ and C5–OC**H**$_2$CH$_3$), 2.12 (6H, *s*, C2–CH$_3$ and C6–CH$_3$), 1.29 (6H, *t*, C2–OCH$_2$C**H**$_3$ and C6–OCH$_2$C**H**$_3$). ^{13}C-NMR (300 MHz, DMSO--d_6, δ / ppm): 155.6, 116.2, 131.2, 139.2 (Ph-OH), 151.4 (C2,6), 45.9 (C4), 101.4 (3,5-**C**OOCH$_2$CH$_3$), 63.3 (3,5-COO**C**H$_2$CH$_3$), 14.1(3,5-COOCH$_2$**C**H$_3$), 18.4 (2,6-CH$_3$).

Diethyl 2, 6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarbo-xylate (1e)

Yield: 69 %; m.p.197 °C; Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 7.48; N, 7.48 %. Found: C, 60.91; H, 7.42; N, 7.41 %. IR (KBr, cm^{-1}): 3364 (N–H str), 3047 (Ar–H), 2953 (C–H str of CH$_3$), 1762 (C=O, ester), 1636 (C–NO$_2$), 814 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 8.13–7.44 (4H, *m*, Ph--ring), 8.14 (1H, *s*, NH of pyridine ring), 4.78 (1H, *s*, C4–H), 4.28 (4H, *q*, C3– –OC**H**$_2$CH$_3$ and C5–OC**H**$_2$CH$_3$), 2.33 (6H, *s*, C2–CH$_3$ and C6–CH$_3$), 1.31 (6H, *t*, C2–OCH$_2$C**H**$_3$ and C6–OCH$_2$C**H**$_3$); ^{13}C-NMR (300 MHz, DMSO-d_6, δ / / ppm): 144.8, 123.6, 126.9, 152.0 (Ph–NO$_2$), 153.2 (C2,6), 44.9 (C4), 103.2 (3,5-**C**OOCH$_2$CH$_3$), 61.8 (3,5-COO**C**H$_2$CH$_3$), 14.5 (3,5-COOCH$_2$**C**H$_3$), 18.9 (2,6-**C**H$_3$).

Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbo-xylate (1f)

Yield: 72 %; m.p. 197 °C; Anal. Calcd. for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90 %. Found: C, 66.87; H, 7.07; N, 3.97 %. IR (KBr, cm^{-1}); 3355 (N–H str), 3033 (Ar–H), 2861 (C–H str of CH$_3$), 1733 (C=O, ester), 819 (Ar–H). ^{1}H--NMR (300 MHz, DMSO-d_6, δ / ppm): 8.25 (1H, *s*, NH of pyridine ring), 5.76– –6.17 (5H, *m*, Ph-ring), 4.70 (1H, *s*, C4–H), 4.22 (4H, *q*, C3–OCH$_2$CH$_3$ and C5– –OCH$_2$CH$_3$), 3.78 (3H, *s*, –OCH$_3$), 2.21 (6H, *s*, C2–CH$_3$ and C6–CH$_3$), 1.23 (6H, *t*, C2–OCH$_2$CH$_3$ and C6–OCH$_2$CH$_3$). ^{13}C-NMR (300 MHz, DMSO-d_6, δ / / ppm): 153.1, 112.6, 128.3, 134.9 (Ph), 158.3 (C2,6), 101.2 (3,5-COOCH$_2$CH$_3$), 61.3 (3,5-COOCH$_2$CH$_3$), 54.7 (Ph–OCH$_3$), 44.6 (C4), 13.8 (3,5-COOCH$_2$CH$_3$), 18.4 (2,6-CH$_3$).

1,4-dydro-2,6-dimethyl-4-(2'-*furyl*) *pyridine 3,5-di- β-naphthamide (2a)

Yield: 63 %; m.p. 170 °C; Anal.Calcd. for $C_{33}H_{26}O_3N_3$: C, 78.34; H, 5.07; N, 8.20 %. Found: C,77.30; H, 4.25; N, 7.99. IR (KBr, cm–1): 3374 (N–H), 3222 (NH—C=O), 3021 (Ar–H), 1091 (N–C–N), 828 (Ar–H). 1H--NMR (300 MHz, CDCl3, δ / ppm): 8.43 (1H, *s*, NH of pyridinering), 8.09 (1H, *d*, C3–CONH and C5–CONH), 7.51 (1H, *d*, 5'-H-furyl) 6.24 (1H, *d*, 4'-H-furyl), 6.24 (1H, *d*, 3'-H-furyl); 5.17 (2H, *s*, C4–H), 2.28 (6H, *s*, C2–CH$_3$ and C6–CH$_3$), 2.02 (1H, *d*, NHCS). ^{13}C-NMR (300 MHz, CDCl$_3$, δ / / ppm): 111.8, 108.3, 143.2, 152.8 (C4 in furyl ring), 105.3 (C3,5 in pyridine ring), 166.2 (C=O), 148.9 (C2,6 in pyridine ring), 35.3 (C4 in pyridine ring), 18.2 (C2,6–CH$_3$ in pyridine ring).

1,4-dihydro-2,6-dimethyl-4-phenyl pyridine3,5-di-β-naphthamide (2b)

Yield: 53 %; m.p. 192 °C; Anal. Calcd. for : $C_{35}H_{28}O_2N_3$,: C,80.45; H, 5.36; N, 8.04%. Found: C, 48.64; H, 5.36; N, 8.02%. IR (KBr, cm^{-1}): 3322 (N–H), 3185 (NH–C=O), 3030 (Ar–H), 1729 (C=O), 1071 (N–C–N), 801 (Ar–H). ^{1}H--NMR (300 MHz, $CDCl_3$, δ / ppm): 8.42 (1H, *s*, NH of pyri-dine ring), 8.14 (1H, *d*, C3–CONH and C5–CONH), 7.40–7.23 (5H, *m*, Ph--ring), 5.24 (2H, *s*, C4–H), 2.39 (6H, *s*, C2–CH_3 and C6–CH_3), 2.10 (1H, *d*, –NHCS). ^{13}C-NMR (300 MHz, $CDCl_3$, δ / ppm): 131.8, 128.3, 131.8, 142.8 (C4 in furyl ring), 108.8 (C3,5 in pyridine ring), 165.6 (C=O), 148.9 (C2,6 in pyridine ring), 35.6 (C4 in pyridine ring), 19.9 (2,6-CH_3 in pyridine ring).

1,4-dihydro-2,6-dimethyl-4-(4'-chloro phenyl) pyridine3,5-di-β-naphthamide (2c)

Yield: 75 %; m.p. 189 °C; Anal. Calcd. for $C_{35}H_{27}O_2N_3Cl$: C, 75.46; H, 4.86; N, 7.54%. Found: C, 74.00; H, 4.44; N, 7.33 %. IR (KBr, cm^{-1}): 3323 (N–H), 3233 (NH_2), 3188 (NH–C=O), 3014 (Ar–H), 1767(C=O), 1057 (N–C–N), 803 (Ar–H), 625 (C–Cl). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 8.44 (1H, *s*, NH of pyridine ring), 8.10 (1H, *d*, C3–CONH and C5–CONH), 7.38–7.14 (5H, *m*, Ph-ring), 5.11 (2H, *s*, C4–H), 2.35 (6H, *s*, C2–CH_3 and C6– CH_3), 2.18 (1H, *d*, –NHCS). ^{13}C-NMR (300 MHz, $CDCl_3$, δ / ppm): 129.7,109.3,144.4, 152.8 (C4 in furyl ring), 106.3 (C3,5 in pyridine ring,166.2 (C=O), 147.9 (C2,6 in pyridine ring), 38.3 (C4 in pyridinering),19.2 (2,6–CH_3 in pyridine ring)

1,4-dihydro-2,6-dimethyl-4-(4'-hydroxy phenyl) pyridine3,5-di-β-naphthamide (2d).

Yield: 74 %; m.p. 201 °C; Anal. Calcd. for $C_{35}H_{28}N_3O_3$: C, 83.39; H, 5.79; N, 8.10%. Found: C, 83.30; H, 5.49; N, 8.03 %. IR (KBr, cm^{-1}): 3332 (N–H), 3182 (NH–C=O), 3018 (Ar–H), 1739 (C=O), 1061 (N– –C–N). ^{1}H-NMR ($CDCl_3$, δ / ppm): 9.31 (1H, *s*, OH), 8.16 (1H, *s*, NH of pyridine ring), 8.09 (1H, *d*, C3–CONH and C5–CONH), 7.39– –7.22 (5H, *m*, Ph-ring), 5.11 (2H, *s*, C4–H), 2.25 (6H, *s*, C2–CH_3 and C6–CH_3), 2.02 (1H, *d*, –NHCS). ^{13}C-NMR (300 MHz, $CDCl_3$, δ / ppm): 155.8, 137.1130.3, 114.2 (C4 in 4-OH-phenyl ring), 103.9 (3,5-C in pyridine ring), 165.9 (C=O), 143.1(C2,6 in pyridine ring), 44.8 (C4 in pyridine ring), 19.2 (2,6–CH_3 in pyridine ring).

1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl) pyridine3,5-di-β-naphthamide (2e)

Yield: 76 %; m.p. 190 °C; Anal. Calcd. for $C_{35}H_{27}N_4O_4$: C, 83.39; H, 5.79; N,8.10%. Found: C, 83.33; H, 5.33; N, 8.00%. IR (KBr, cm^{-1}): 3310 (N–H), 3218 (NH–C=O), 3041 (Ar–H), 1710 (C=O), 1530 (C–NO_2), 1094 (N–C–N). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 8.60 (1H, *s*, NH of pyridine ring), 8.15 (1H, *d*, C3–CONH and C5–CONH), 7.42–7.18 (5H, *m*, Ph-ring), 5.17 (2H, *s*, C4–H), 2.31 (6H, *s*, C2–CH_3 and C6–CH_3), 2.08 (1H, *d*, –NHCS). ^{13}C-NMR (300 MHz, $CDCl_3$, δ / ppm): 143.2, 123.7, 126.7 (C4 in 4--NO_2-phenyl ring), 102.9 (3,5-C in pyridine ring), 164.9 (C=O), 149.9 (2,6-C in pyridine ring), 44.5 (4-C in pyridine ring), 19.7(2,6-C–**C**H_3 in pyridine ring).

1,4-dihydro-2,6-dimethyl-4-(4'-methoxy phenyl) pyridine3,5-di-β-naphthamide (2f)

Yield: 67 %; m.p. 185 °C; Anal. Calcd. for $C_{36}H_{30}O_3N_3$: C, 78.26; H, 5.74; N, 8.04 %. Found: C, 78.23; H, 5.09; N, 8.01%. IR (KBr, cm^{-1}): 3323 (N–H), 3251 (NH– C=O), 3034 (Ar–H), 1717 (C=O), 1091 (N-C-N), 808 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 8.57 (1H, *s*, N–H of pyridine ring), 8.05 (1H, *d*, C3–CONH and C5–CONH), 7.33–7.27 (5H, *m*, Ph-ring), 5.21 (2H, *s*, C4–H), 3.81 (3H, *s*, –OCH_3), 2.25 (6H, *s*, C2–CH_3 and C6–CH_3), 2.10 (1H, *d*, –NHCS). ^{13}C-NMR (300 MHz, $CDCl_3$, δ / ppm): 111.8, 108.3, 143.2, 152.8 (C4 in 4-CH_3O-phenyl ring), 105.3 (3,5-C in pyridine ring), 166.2 (3,5-C=O), 147.7 (2,6-C in pyridine ring), 44.7 (C4 in pyridine ring), 18.8 (2,6-CH_3 in pyridine ring), 55.9 (–OCH_3).

RESULTS AND DISCUSSION

The IR spectra of compounds **1a**–**f** showed an absorption band at 3332 to 3354 cm^{-1} due to N–H stretching, another absorption band at 1741–1764 cm^{-1} due to the keto group in the ester groups. Compound **1c** showed an absorption band at 610 cm^{-1} corresponding the to Cl–C bonds, compound **1d** showed an absorption band at 1447 cm^{-1} corresponding to the HO–C bonds and compound **1e** showed an absorption band at 1536 cm^{-1} corresponding the O_2N–C groups. The ^{1}H-NMR spectra of compounds **1a**–**f** showed a singlet at δ 8.11–8.41 ppm, attributable to the NH protons present in the 1,4-dihydropyridine ring, and another important singlet at δ 4.67–4.79 ppm, which was attributable to the C4–H proton present in the 1,4-dihydropyridine ring. The ^{13}C-NMR spectra of compounds **1a**-**f**showed peaks at δ 33.2–44.9 ppm, corresponding to C4 in the pyridine ring, δ 101.4–103.9 ppm, corresponding to the 3,5-position of C–**C**OOEt, and δ 150.7– –152.8 ppm, corresponding to the 2,6-position of **C**–CH_3 in the pyridine ring. The IR spectra of compounds **2a**–**f** showed an absorption band obtained at 3320–3372 cm^{-1} corresponding to the NH group present in the 1,4-dihydropyridine ring and another absorption band at 3118–3200 cm^{-1} which was due to NH–C=O stretching. An absorption band for the C=S group was observed at 1242–1272 cm^{-1}. The ^{1}H--NMR spectra of **2a**–**f** showed as a singlet a band at δ 8.41–8.64 ppm, attributable to the NH protons present in the 1,4-dihydropyridine ring. The C4–H, CONH, and NHCS protons resonated as singlets at δ 5.10–5.21, 8.01–8.15,and 2.02– –2.12 respectively. The ^{13}C-NMR spectra of compounds **2a**–**f** showed peaks at δ 163.1–166.2, 181.1–184.6, 34.6–46.5 and 18.2–19.7 ppm, corresponding to the 3,5-position of CO-NH group in the pyridine ring, the 3,5--position of CS in the pyridine ring, the 4-position of carbon in the pyridine ring and the 2,6-position of CH_3 in the

pyridine ring, respectively. Mass spectral analysis of compounds **2a–f** showed molecular ion peaks, which confirmed the molecular masses of these compounds. The structure determination was done using physical and spectral data, and by comparison with data reported in the literature[18-23]

Antibacterial screening:

The bacterial zones of inhibition values (mm) are given in Table I. The antimicrobial activities of compounds **1a–f** and **2a–f** were screened. The structure activity relationship analysis of the base compounds **1a–f** was compared with that of the thiosemicarbazone-containing compounds **2a–f**. Ciprofloxacin was used as a standard at 100 µg ml^{-1}. Compounds **1a–f** showed low activity compared with compounds **2a–f** towards all the tested organisms.

Table 1: Antibacterial activity of the synthesized compounds 1a–f and 2a–f (disk diameter: 7 cm)

Compound	*S. aureus*	*b.Subtillus*	*e. coli*	*Vibreocholerae*
la	-	-	11	13
lb	6	6	16	17
lc	9	-	18	13
Id	6	-	-	-
le	7	6	6	18
If	8	-	5	13
2a	5	6	15	25
2b	19	18	12	15
2c	24	16	14	12
2d	15	12	25	-
2e	13	11	16	22
2f	11	19	17	20
Ciprofloxacin	24	21	23	13

Antifungal screening:

The fungacidal zones of inhibition, mm, values are given in Table II. Compounds **2a–f** were screened for *Aspergillus niger*; the compounds **2b–f** were less active compared with the standard clotrimazole, while compound **2a** had no activity Compounds **2a–f** were screened for *Candida albicans*. Compound **2d** was hifhly active compared with the standard clotrimazole because it contained an amide froup in the 3,5-position and 4-hydroxyphenyl in the fourth position, while the other compounds **2a–c** and **2e–f** had lower activities than the standard clotrimazolCompounds **2a–f** were screened for *Microsporum audouinii*. The compounds **2a** and **2c–f** had lower activity than the standard clotrimazole, while compound **2b** was inactive Compounds **2a–f** were screened for *Cryptococcus neoformans*, the compound **2f** had equipotent activity with the standard clotrimazole, while the other compounds **2a–d** and **2e** had lower activities compared with the standard clotrimazole and compound **2f** exhibited no activity

Table- II: Antifungal activity of the synthesized compounds 1a–f and 2a–f (disk diameter: 7 cm)

Compound	*Trichoderma Sp*	*A. niger*	*A.Parasitica*	**Chrysosporium Sp**
la	10	12	16	-
lb	11	9	7	8
lc	12	15	12	7
Id	14	-	13	8
le	7	-	-	-
If	12	14	13	12
2a	-	15	7	18
2b	12	-	5	7
2c	12	25	16	11
2d	25	26	20	19
2e	9	16	19	15
2f	15	17	11	24
Clotrimazole	12	23	22	12

CONCLUSION

A new series of 1,4-dihydropyriodine derivatives (**2a**-**f**) was synthesized. The synthesized compounds were screened for their antibacterial activity, whereby compound **2d** was more active than ciprofloxacin against *b.Subtillus* organism. When the synthesized compounds were screened for their antifungal activity, a compound **2d** showed higher activity than clotrimazole against *A.Parasitica.* These findings could be of importance for further studies in this field.

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