Scientific Reviews
&
Chemical Communications

Sci. Revs. Chem. Commun.: 3(3), 2013, 141-149
ISSN 2277-2669

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME 1,4-DIHYDROPYRIDINES DERIVATIVES

N. SRINIVASA RAO[*] and K. LAKSHMI[a]

Department of Chemistry, Bapatla Engineering College, BAPATLA – 522101 (A.P.) INDIA
[a]Department of Chemistry, Tirumala Engineering College, NARASARAOPET – 522601 (A.P.) INDIA

(*Received : 17.06.2013; Accepted : 04.07.2013*)

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 α-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, Antimicrobial activity.

INTRODUCTION

1, 4-Dihydropyridines (1, 4-DHPs) are important class of compounds in the field of drugs and pharmaceuticals[1-3]. Hantzsch 1,4-dihydropyridines (di alkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates) are widely used clinically as calcium channel blockers for the treatment of cardiovascular diseases, such as, nifedipine and nitrendipine are used for the treatment of hypertension and angina pectoris, nislodipine is a potent vasodilator and nimodipine exhibits selectivity for cerebral vasculature[4]. DHP derivatives are employed as potential drug candidates for the treatment of congestive heart failure[5]. The success of those calcium antagonists has led to the development of novel synthetic strategies to improve their classical methods of preparation[6,7].

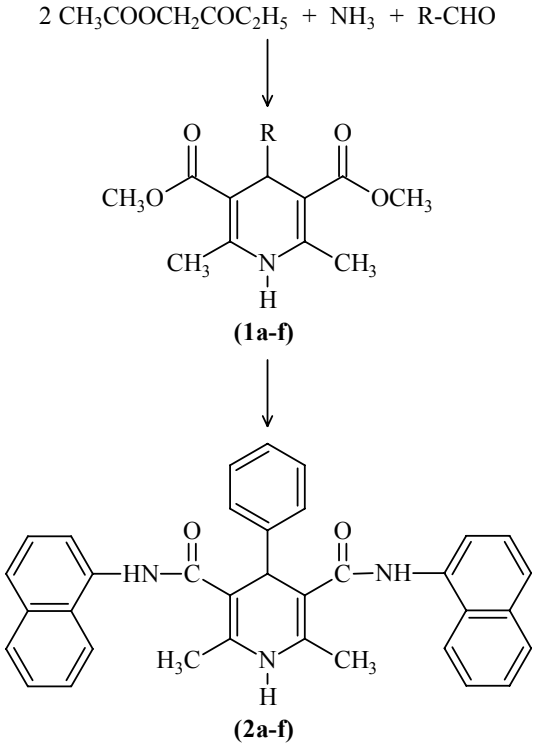
1,4-DHPs are generally synthesized by classical Hantzsch reaction, which involves the condensation of an aldehyde, -ketoester and ammonia or ammonium acetate in refluxing ethanol or other lower alcohols. A number of improved methods have been reported in the literature to modify this reaction[8]. In recent years, clay catalysts, particularly montmorillonitehave received considerable attention in chemical synthesis[9]. They are inexpensive, non-corrosive and recyclable. Thus the montmorillonite-catalysed procedures have many advantages, such as environmental compatibility and easy handling. Recently, we reported the Hantzsch synthesis of 1, 4-dihydropyridine derivatives catalysed[10] by montmorillonite K10.

Now a days there is an increasing awareness of urgent necessity to limit, as far as possible, any source of pollution. Facing up to these facts, chemists have to dedicate numerous efforts to the development

Available online at www.sadgurupublications.com
[*]Author for correspondence; E-mail: drsrinunathani@yahoo.co.in

of clean technologies. This new challenge has led to growing interest in the displacement of organic reaction in aqueous media[11,12] and solvent free conditions[13,14].

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[15-17]



1a, 2a : R = 2-Furyl
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

Scheme

EXPERIMENTAL

1,4 dihydro-2,6-dimethyl-4-(aryl substituted) pridine-3,5-dicarboxylic acid dimethyl ester (1a-f)

To a solution of aromatic aldehyde in ethanol (0.03 mol), methyl acetoacetate (0.06 mol) and liquid ammonia (5 mL) were added. The mixture was refluxed for 4 hours 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) (0.01 mol) and α-napthal amine (0.02 mol) in 1,4 dioxane (25 mL) were refluxed for 7 hours povred crushed ice. The soiled formed is recrystillised 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}): 3352 (N–H str), 3030 (Ar–H), 2940 (C–H str of CH_3), 1745 (C=O, ester), 810 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 8.30 (1H, *s*, NH of pyridine ring), 7.37 (1H, *s*, furyl ring), 6.10–6.47 (2H, *d*, furyl ring), 4.22 (1H, *s,* C4–H), 4.20 (4H, *q*, C3– $-CH_2CH_3$ and C5–OCH_2CH_3), 2.31 (6H, *s*, C2–CH_3 and C6–CH_3), 1.34 (6H, *t,* C2–OCH_2CH_3 and C6–OCH_2CH_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--$COOCH_2CH_3$), 62.1 (3,5-$COOCH_2CH_3$), 15.9 (3,5-$COOCH_2CH_3$), 18.3 (2,6--CH_3).

Diethyl 2,6-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–OCH_2CH_3 and C5– –OCH_2CH_3), 2.28 (6H, *s*, C2–CH_3 and C6-CH_3), 1.32 (6H, *t*, C2–OCH_2CH_3 and C6–OCH_2CH_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-$COOCH_2CH_3$), 62.1 (3,5--$COOCH_2CH_3$), 44.1 (C4), 19.1 (2,6-CH_3), 15.4 (3,5-$COOCH_2CH_3$).

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_2CH_3 and C5–OCH_2CH_3), 2.19 (6H, *s,* C2–CH_3 and C6–CH_3), 1.33 (6H, *t*, C2–OCH_2CH_3 and C6–OCH_2CH_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--$COOCH_2CH_3$), 60.4 (3,5-$COOCH_2CH_3$), 15.5 (3,5-$COOCH_2CH_3$), 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–OCH_2CH_3 and C5–OCH_2CH_3), 2.12 (6H, *s,* C2–CH_3 and C6–CH_3), 1.29 (6H, *t*, C2–OCH_2CH_3 and C6–OCH_2CH_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-$COOCH_2CH_3$), 63.3 (3,5-$COOCH_2CH_3$), 14.1(3,5-$COOCH_2CH_3$), 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– –OCH_2CH_3 and C5–OCH_2CH_3), 2.33 (6H*, s,* C2–CH_3 and C6–CH_3), 1.31 (6H, *t,* C2–OCH_2CH_3 and C6–OCH_2CH_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-$COOCH_2CH_3$), 61.8 (3,5-$COOCH_2CH_3$), 14.5 (3,5-$COOCH_2CH_3$), 18.9 (2,6-CH_3).

Diethyl4-(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_2CH_3 and C5– –OCH_2CH_3), 3.78 (3H, *s*, –OCH_3), 2.21 (6H, *s,* C2–CH_3 and C6–CH_3), 1.23 (6H, *t,* C2–OCH_2CH_3 and C6–OCH_2CH_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-$COOCH_2CH_3$), 61.3 (3,5-$COOCH_2CH_3$), 54.7 (Ph–OCH_3), 44.6 (C4), 13.8 (3,5-$COOCH_2CH_3$), 18.4 (2,6-CH_3).

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

Yield: 63%; m.p. 161°C; Anal.Calcd. for $C_{33}H_{26}O_3N_3$: C, 77.34; H, 5.07; N, 8.20%. Found: C,77.30; H, 4.25; N, 7.99. IR (KBr, cm^{-1}): 3372 (N–H), 3200 (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-α-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}): 3320 (N–H), 3185 (NH–C=O), 3030 (Ar–H), 1720 (C=O), 1071 (N–C–N), 801 (Ar–H). ^{1}H--NMR (300 MHz, $CDCl_3$, δ / ppm): 8.41 (1H, *s*, NH of pyri-dine ring), 8.15 (1H, *d*, C3–CONH and C5–CONH), 7.40–7.23 (5H, *m*, Ph--ring), 5.25 (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-α-naphthamide (2c)

Yield: 75%; m.p. 180°C; Anal. Calcd. for $C_{35}H_{27}O_2N_3Cl$: C, 75.47; H, 4.85; 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-α-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-α-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–CH_3 in pyridine ring).

1,4-dihydro-2,6-dimethyl-4-(4'-methoxy phenyl) pyridine3,5-di-α-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).

Spectroscopy

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.

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 (SAR) 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	-	-	10	15
lb	5	6	6	7
lc	10	-	8	11
Id	5	-	-	-
le	6	6	6	12
If	6	-	5	14
2a	8	6	15	29
2b	18	17	11	16
2c	24	14	14	11
2d	14	15	26	-
2e	14	13	15	21
2f	12	17	16	21
Ciprofloxacin	23	20	26	31

Compounds **2a–f** were screened for *Staphylococcus aureus* and compound **2c** was found to be highly active compared with the standard ciprofloxacin because it contained an amide group in the 3,5-position with 4-chloro-phenyl group in the fourth position. On the other hand, compounds **2a**, **2b** and **2d–f** had low activities compared with the standard ciprofloxacin.

Compounds **2a–f** were screened for *Bacillus subtillus*, whereby compounds **2b** and **2f** showed equipotent activity with the standard ciprofloxacin. On the other hand, compounds **2a**, **2d–e** and **2f** had low activities compared with the standard ciprofloxacin.

Compounds **2a–f** were screened for *Escherichia coli* and the compound **2d** was found to have an equipotent activity compared with the standard ciproflo-xacin. On the other hand, compounds **2a–c** and **2e–f** had low activities compared with the standard ciprofloxacin.

Compounds **2a–f** were screened for *Vibreocholerae*, whereby the compound **2a** exhibited equipotent activity compared with the standard cipro-floxacin, while the other compounds **2b–f** had low activities compared with the standard ciprofloxacin.

Antifungal screening

The fungacidal zones of inhibition, mm, values are given in Table 2. 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 clotrimazole.

Table 2: 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	8	-	10	-
lb	10	9	7	8
lc	11	15	-	7
Id	15	-	13	8
le	8	-	-	-
If	12	14	12	10
2a	-	9	7	8
2b	11	-	5	7
2c	14	21	15	14
2d	15	26	18	15
2e	9	12	16	14
2f	10	16	19	23
Clotrimazole	26	23	26	24

Compounds **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 clotri-mazole and compound **2f** exhibited no activity.

Chemistry

The melting points were recorded in open capillary tubes and are reported uncorrected. The IR spectra were recorded in KBr on a Shimadzu 8201pc FTIR specrometer (4000–400 cm^{-1}). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DRX-300 MHz instrument. The mass spectra (EI) were obtained on a Jeol JMS D-300 spectrometer operating at 70 eV. Elemental analyses (C, H, N and S) were realized using an Element Analyzer, Model Vario EL III. The purity of the compounds was checked by thin layer chromatography (TLC)

In vitro antibacterial screening

The compounds **la-f** and **2a-f** were evaluated for their *in vitro* antibacterial activity against *S. aureus* (ATCC-25923), b.Subtillus (recultured), *E. coli* (ATCC-25922) and *Vibreocholerae* (ATCC-27853) by the agar diffusion method[18,19] using Mueller-Hinton agar (Hi--Media) medium. Each compound was tested at a concentration of 100 ug mL^{-1} in DMSO. Ciprofloxacin was used as the standard. The zone of inhibition (mm) was measured after 24 h incubation at 37ºC.

In vitro antifungal screening

The compounds **la-f** and **2a-f** were evaluated for their *in vitro* antifungal activity against *Trichoderma Sp, A. niger, A. Parasitica* and *Chrysosporium Sp* (recultured) using an agar diffusion method[20,21] with Sabouraud's dextrose agar (Hi-Media). Each compound was tested at a concentration of

100 ug mL^{-1} in DMSO. Clotrimazole was used as the standard. The zone of inhibition (mm) was measured after 24 h incubation at 37°C.

CONCLUSION

A new series of 1,4-dihydropyriodine derivatives **2a-f** was synthesized. The synthesized compounds were screened for their antibacterial activity, whereby compound **2c** 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.

REFERENCES

1. G. M. Reddy, M. Shiradkar and A. K. Chkravarthy, Curr. Org. Chem., **11**, 847 (2007).
2. F. Bossert, F. Mayer and E. Wehinger, Angew Chem. Int. Ed. Engl., **20**, 762 (1981).
3. R. A. Janis and D. J. Triggle, J. Med. Chem., **25**, 775 (1983).
4. R. H. Bocker and F. P. Guengerich, J. Med. Chem., **29**, 1596 (1986).
5. D. Vo, W. C. Matowe, M. Ramesh, N. Iqbal, M. W. Wolowyk, S. E. Howlett and E. E. Knaus, Med. Chem., **38**, 2851 (1995).
6. M. F. Gordeev, D. V. Patel and E. M. Gordon, J. Org. Chem., **61**, 924 (1996).
7. J. G. Breitenbucher and G. Figliozzi**,** Tetrahedron Lett., **41**, 4311 (2000).
8. (a) M. A. Chari and K. Syamasundar, Catal. Commun., **6**, 624 (2005).
   (b) J. L. Donelson, R. A. Gibbs and S. K. De, J. Mol. Catal. A Chem., **256**, 309 (2006).
   (c) L. M. Wang, J. Sheng, L. Zhang, J. W. Han, Z. Y. Fan, H. Tian and C-T Qian, Tetrahedron, **61**, 1539 (2005).
   (d) J. H. Lee, Tetrahedron Lett., **46**, 7329 (2005)
   (e) S. Ko, M. N. V. Sastry, C. Lin and C. F. Yao, Tetrahedron Lett., **46**, 5771 (2005).
   (f) R. K. Vohra, C. Bruneau and J. L. Renaud, Adv. Synth. Catal., **384**, 2571 (2006).
   (g) S. Kikuchi, M. Iwai, H. Murayama and S. I. Fukuzawa, Tetrahedron Lett., **49**, 114 (2008).
9. R. S. Varma, Tetrahedron, **58**, 1235-1255 (2002).
10. Z. A. Moshtaghi and H. S. Baradaran, Synth Commun., **38(2)**, 290 (2008).
11. C. J. Li and T. H. Chan, Organic Reaction in Aqueous Media, John Wiley and Sons : New York, NY (1997).
12. U. M. Lindstrom, Chem. Rev., **102**, 2751 (2002).
13. Z. X. Wang and H. L. Qin, Green Chem., **6**, 90 (2004).
14. K. Yoshizawa, S. Toyota and F. Toda, Green Chem., **4**, 68 (2002).
15. H. Salehi and Q. X. Guo, Synth Commun., **34(23)**, 4349 (2004).
16. D. Q. Shi, C. X. Yu and D. Y. Zhuang, J. Chem. Res., **8**, 441 (2008).
17. V. G. Sadvilkar, B. M. Khadilkar and V. G. Gaikar, J. Chem. Technol. Biotechnol., **63(1)**, 33 (2004).

18. W. Bauer, W. M. Kirby, J. C. S. Harris and J. C. Turck, Am. Clin. Pathol. **39**, 493 (1966).

19. R. G. Petersdorf and J. C. Sherris, Am. J. Med., **39**, 766 (1965).

20. S. H. Gillespie, Medical Microbiology-Illustrated, Butterworth Heinemann, London (1994) p. 234.

21. R. S. Varma, Antifungal Agents: Past, Present and Future Prospects, National Academy of Chemistry and Biology, Lucknow (1998).