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Synthesis and antimicrobial activity of a new series of 1,4-dihydropyridine derivatives

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Abstract: A series of 1,4-dihydropyridine derivatives (**1a**–**g**) were prepared from Hantzsch syntheses. The compounds **1a**–**g** were reacted with thiosemicarbazide to give the new series of compounds **2a**–**g**. IR, ^{1}H-NMR, ^{13}C-NMR, mass spectral and elemental analysis confirmed the synthesized compounds. The synthesized compounds were also screened for their antimicrobial activity.

Keywords: 1,4-dihydropyridine; thiosemicarbazide; condensation; antimicrobial activity.

INTRODUCTION

1,4-Dihydropyridine derivatives are of interest because of their biological activity, such as vasodilators, antihypertensive,[1–4] anti-inflammatory,[5] antihypoxic and anti-ischemic agents[6] and calcium channel modulators of the nifedipine type.[7] Recently, it was reported that the amide group was involved in the 3,5-position of 1,4-dihydropyridine derivatives and it exhibited pharmacological effects.[8,9] Basically thiosemicarbazone containing heterocyclics have significant biological activity, such as antitumour, fungicidal, bactericidal, anti-inflammatory and antiviral activities.[10–13] In view of these observations, it was decided to synthesize a new series of 1,4-dihydropyridine derivatives (**2a**–**g**) and screen them for their level of antimicrobial activity.

RESULTS AND DISCUSSION

Chemistry

The series of diethyl 2,6-dimethyl-4-substituted phenyl-1,4-dihydropyridine--3,5-dicarboxylate (**1a**–**f**) are already published in literature[14–19], but not their

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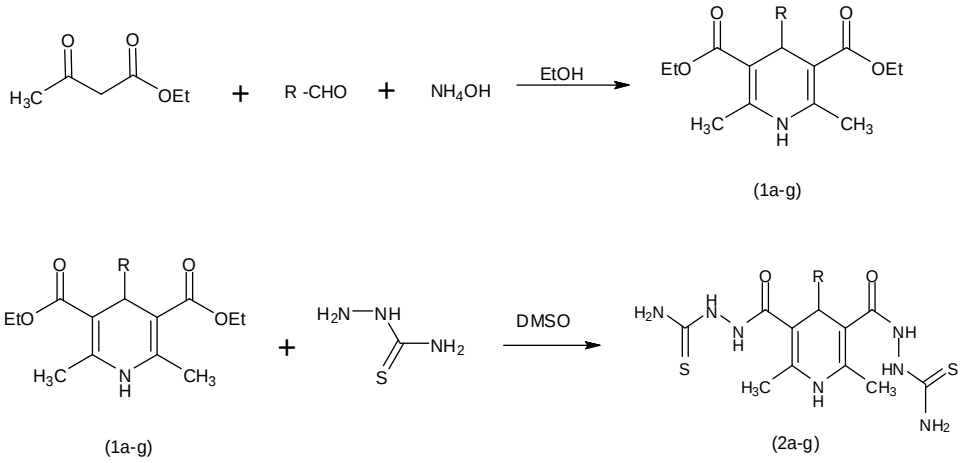
antimicrobial screening. On the other hand the syntheses and antimicrobial screening of compound **1g** has not been published. The compounds **1a**–**g** were reacted with thiosemicarbazide to give 4-aryl-2,6-dimethyl-1,4-dihydropyridine--3,5-dicarboxylic acid, 3,5-bis[2-(aminothioxomethyl)hydrazide] (**2a**–**g**) by the hydrazinolysis method[20,21] (Scheme 1).



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

1g, 2g : R = 4-$(CH_3)_2N$-C_6H_4

Scheme 1. Synthesis of the compounds **2a**–**g**.

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}): 3349 (N–H str), 3030 (Ar–H), 2940 (C–H str of CH_3), 1745 (C=O, ester), 812 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 8.20 (1H, *s*, NH of pyridine ring), 7.27 (1H, *s*, furyl ring), 6.10–6.27 (2H, *d*, furyl ring), 4.72 (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, 110.6, 106.7, 152.5 (furyl ring), 151.8 (C2,6), 33.2 (C4), 102.3 (3,5-

-**C**OOCH$_2$CH$_3$), 61.1(3,5-COO**C**H$_2$CH$_3$), 14.9 (3,5-COOCH$_2$**C**H$_3$), 18.1 (2,6--**C**H$_3$). MS (*m*/*z* (relative abundance, %)): 320.15 (M^++1, 40.2), 275.29, 231.24, 203.23, 173.22, 161.20, 147.2, 134.12, 82.10.

*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–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$_3$). MS (*m*/*z* (relative abundance, %)): 330.39 (M^++1, 38.9), 285.33, 241.28, 185.26, 171.23, 157.21, 81.11, 68.11.

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**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}): 3332 (N–H str), 3074 (Ar–H), 2942 (C–H str of CH_3), 1741 (C=O, ester), 812 (Ar–H), 610 (C–Cl), 787 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 8.31 (1H, *s*, NH of pyridine ring), 7.36–7.19 (5H, *m*, Ph-ring), 4.76 (1H, *s*, C4–H), 4.18 (4H, *q*, 3C–OC**H**$_2$CH$_3$ and C5–OC**H**$_2$CH$_3$), 2.21 (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): 131.4, 128.1, 130.8, 142.5 (Ph–Cl), 152.5 (C2,6), 34.6 (C4), 103.9 (3,5--**C**OOCH$_2$CH$_3$), 60.3 (3,5-COO**C**H$_2$CH$_3$), 15.2 (3,5-COOCH$_2$**C**H$_3$), 18.6 (2,6--CH$_3$). MS (*m*/*z* (relative abundance, %)): 364.90 (M^++1, 21.2), 275.57, 219.70, 185.26, 171.23, 157.21, 144.21

*Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**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), 3024 (Ar–H), 2922 (C–H str of CH_3), 1764 (C=O, ester), 1447 (C–OH), 814 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 9.47 (1H, *s*, C–OH), 8.41 (1H, *s*, NH of pyridine ring), 6.34–7.07 (4H, *m*, Ph-ring), 4.67 (1H, *s*, C4–H), 4.28 (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$_3$), 1.28 (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, 138.2 (Ph-OH), 151.4 (C2,6), 44.9 (C4), 101.4 (3,5-**C**OOCH$_2$CH$_3$), 62.3 (3,5-COO**C**H$_2$CH$_3$), 14.1(3,5-COOCH$_2$**C**H$_3$), 18.4 (2,6-CH$_3$). MS (*m*/*z* (relative abundance, %)): 346.81 (M^++1, 12.3), 310.45, 257.81, 201.48, 187.22, 173.28, 157.21.

*Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**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}): 3354 (N–H str), 3037 (Ar–H), 2973 (C–H str of CH_3), 1762 (C=O, ester), 1536 (C–NO_2), 812 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 8.13–7.47 (4H, *m*, Ph--ring), 8.11 (1H, *s*, NH of pyridine ring), 4.79 (1H, *s*, C4–H), 4.25 (4H, *q*, C3––OC**H**$_2$CH$_3$ and C5–OC**H**$_2$CH$_3$), 2.31 (6H, *s*, C2–CH_3 and C6–CH_3), 1.37 (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, 151.0 (Ph–NO_2), 152.2 (C2,6), 43.9 (C4), 103.2 (3,5-**C**OOCH$_2$CH$_3$), 60.8 (3,5-COO**C**H$_2$CH$_3$), 14.4 (3,5-COOCH$_2$**C**H$_3$), 18.8 (2,6-**C**H$_3$). MS (*m*/*z* (relative abundance, %)): 375.22 (M^++1, 21.2), 286.26, 185.26, 171.23, 157.21.

*Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**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}); 3352 (N–H str), 3026 (Ar–H), 2961 (C–H str of CH_3), 1742 (C=O, ester), 823 (Ar–H). ^{1}H--NMR (300 MHz, DMSO-d_6, δ / ppm): 8.21 (1H, *s*, NH of pyridine ring), 6.86––7.17 (5H, *m*, Ph-ring), 4.69 (1H, *s*, C4–H), 4.23 (4H, *q*, C3–OC**H**$_2$CH$_3$ and C5––OC**H**$_2$CH$_3$), 3.84 (3H, *s*, –OCH$_3$), 2.23 (6H, *s*, C2–CH_3 and C6–CH_3), 1.30 (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): 157.2, 114.6, 129.3, 135.9 (Ph), 158.3 (C2,6), 102.3 (3,5-**C**OOCH$_2$CH$_3$), 61.5 (3,5-COO**C**H$_2$CH$_3$), 55.7 (Ph–O**C**H$_3$), 43.6 (C4), 14.8 (3,5-COOCH$_2$**C**H$_3$), 18.0 (2,6-CH_3). MS (*m*/*z* (relative abundance, %)): 360.44 (M^++1, 41.2), 331.81, 287.31, 243.25, 187.23, 157.21.

*Diethyl 4-(4-(dimethylamino)phenyl)-2,6–dimethyl-1,4-dihydropyridine-3,5--dicarboxylate (**1g**)*. Yield: 56 %; m.p. 227 °C; Anal. Calcd. for $C_{21}H_{28}N_2O_4$: C, 67.72; H,7.58; N, 7.52 %. Found: C, 67.77; H, 7.52; N, 7.58 %. IR (KBr, cm^{-1}): 3348 (N–H str), 3027 (Ar–H), 2956 (C–H str of CH_3), 1761 (C=O, ester), 808 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 8.37 (1H, *s*, NH of pyridine ring), 7.28–7.21 (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$_3$), 3.12 (6H, *s*, –N(CH$_3$)$_2$), 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): 128.3, 112.9, 148.5, 133.9 (Ph), 151.8 (C2,6), 43.8 (C4), 102.8 (3,5-**C**OOCH$_2$CH$_3$), 60.5 (3,5-COO**C**H$_2$CH$_3$), 40.8 (–N(**C**H$_3$)$_2$), 13.9 (3,5-COOCH$_2$**C**H$_3$), 18.9 (2,6-**C**H$_3$). MS (*m*/*z* (relative abundance, %)): 373.44 (M^++1, 51.8), 284.35, 228.33, 185.26, 171.23, 157.21.

*4-(Furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid, 3,5--bis[2-(aminothioxomethyl)hydrazide] (**2a**)*. Yield: 63 %; m.p. 161 °C; Anal. Calcd. for $C_{15}H_{19}N_7O_3S_2$: C, 44.00; H, 4.68; N, 23.94 ; S, 15.66 %. Found: C, 44.06; H, 4.62; N, 23.97; S, 15.62 %. IR (KBr, cm^{-1}): 3372 (N–H), 3200 (NH––C=O), 3218 (NH_2), 3021 (Ar–H), 1260 (C=S), 1091 (N–C–N), 828 (Ar–H). ^{1}H--NMR (300 MHz, $CDCl_3$, δ / ppm): 9.62 (2H, *s*, NH_2), 8.43 (1H, *s*, NH of pyridine ring), 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), 182.1 (C=S), 148.9 (C2,6 in pyridine ring), 35.3 (C4 in pyridine ring), 18.2 (C2,6–CH_3 in pyridine ring); MS (*m/z*, (relative abundance, %)): 410 (M^++1, 30.2), 291.30, 161.27, 175.22, 147.12, 81.11.

*2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid, 3,5-bis[2--(aminothioxomethyl)hydrazide] (**2b**)*. Yield: 53 %; m.p. 192 °C; Anal. Calcd. for $C_{17}H_{21}N_7O_2S_2$: C, 48.67; H, 5.50; N, 23.37; S, 15.29 %. Found: C, 48.64; H, 5.57; N, 23.31; S, 15.34 %. IR (KBr, cm^{-1}): 3370 (N–H), 3175 (NH–C=O), 3218 (NH_2), 3034 (Ar–H), 1718 (C=O), 1260 (C=S), 1091 (N–C–N), 808 (Ar–H). ^{1}H--NMR (300 MHz, $CDCl_3$, δ / ppm): 9.60 (2H, *s*, NH_2), 8.40 (1H, *s*, NH of pyridine ring), 8.11 (1H, *d*, C3–CONH and C5–CONH), 7.39–7.22 (5H, *m*, Ph--ring), 5.20 (2H, *s*, C4–H), 2.37 (6H, *s*, C2–CH_3 and C6–CH_3), 2.12 (1H, *d*, –NHCS); ^{13}C-NMR (300 MHz, $CDCl_3$, δ / ppm): 131.3, 128.5, 130.9, 141.8 (C4 in furyl ring), 106.8 (C3,5 in pyridine ring), 164.6 (C=O), 182.8 (C=S), 147.9 (C2,6 in pyridine ring), 34.6 (C4 in pyridine ring), 18.9 (2,6-CH_3 in pyridine ring); MS (*m/z*,(relative abundance, %)): 420.20 (M^++1, 20.1), 301.34, 241.28, 185.2, 157.21, 81.11.

*4-(4-Chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid, 3,5-bis[2-(aminothioxomethyl)hydrazide] (**2c**)*. Yield: 68 %; m.p. 194 °C; Anal. Calcd. for $C_{17}H_{20}ClN_7O_2S_2$: C, 4.98; H, 4.40; N, 21.60; S, 14.14 %. Found: C, 44.92; H, 4.46; N, 21.64; S, 14.18 %. IR (KBr, cm^{-1}): 3325 (N–H), 3231 (NH_2), 3198 (NH–C=O), 3024 (Ar–H), 1265 (C=S), 1707(C=O), 1097 (N–C–N), 810 (Ar–H), 623 (C–Cl). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 9.41 (2H, *s*, NH_2), 8.41 (1H, *s*, NH of pyridine ring), 8.11 (1H, *d*, C3–CONH and C5–CONH), 7.38–7.14 (5H, *m*, Ph-ring), 5.10 (2H, *s*, C4–H), 2.45 (6H, *s*, C2–CH_3 and C6–CH_3), 2.08 (1H, *d*, –NHCS). ^{13}C-NMR (300 MHz, $CDCl_3$, δ / ppm): 128.7, 108.3, 143.2, 152.8 (C4 in furyl ring), 105.3 (C3,5 in pyridine ring), 166.2 (C=O), 182.1 (C=S), 148.9 (C2,6 in pyridine ring), 39.3 (C4 in pyridine ring), 18.2 (2,6–CH_3 in pyridine ring); MS (*m/z* (relative abundance, %)): 454.12 (M^++1, 12.3), 335.78, 275.73, 219.70, 157.21, 81.11.

*4-(4-Hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid, 3,5-bis[2-(aminothioxomethyl)hydrazide] (**2d**)*. Yield: 74 %; m.p. 201 °C; Anal. Calcd. for $C_{17}H_{21}N_7O_3S_2$: C, 46.88; H, 22.51; N, 4.86; S, 14.72 %. Found: C, 46.81; H, 22.57; N, 4.81; S, 14.77 %. IR (KBr, cm^{-1}): 3342 (N–H), 3220 (NH_2), 3192 (NH–C=O), 3028 (Ar–H), 1472 (C–OH), 1717 (C=O), 1242 (C=S), 1091 (N––C–N). ^{1}H-NMR ($CDCl_3$, δ / ppm): 9.71 (2H, *s*, NH_2), 9.41 (1H, *s*, OH), 8.64 (1H, *s*, NH of pyridine ring), 8.01 (1H, *d*, C3–CONH and C5–CONH), 7.33––7.27 (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, 137.1,

130.3, 114.2 (C4 in 4-OH-phenyl ring), 102.9 (3,5-C in pyridine ring), 164.9 (C=O), 184.6 (3,5 C=S), 148.1(C2,6 in pyridine ring), 43.8 (C4 in pyridine ring), 19.2 (2,6–CH_3 in pyridine ring). MS (*m*/*z* (relative abundance, %)): 435.52 (M^++1, 27.2), 257.28, 201.26, 173.21, 157.21, 81.11.

*2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid, 3,5-bis[2-(aminothioxomethyl)hydrazide] (**2e**)*. Yield: 76 %; m.p. 190 °C; Anal. Calcd. for $C_{17}H_{20}N_8O_4S_2$: C, 43.96; H, 4.34; N, 24.12; S, 15.81 %. Found: C, 43.91; H, 4.38; N, 24.17; S, 15.87 %. IR (KBr, cm^{-1}): 3310 (N–H), 3241 (NH_2), 3218 (NH–C=O), 3041 (Ar–H), 1710 (C=O), 1530 (C–NO_2), 1272 (C=S), 1094 (N–C–N). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 9.77 (2H, *s*, NH_2), 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), 181.9 (C=S), 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). MS (*m*/*z* (relative abundance, %)): 465.52 (M^++1, 12.78), 346.34, 286.20, 258.23, 230.21, 202.20, 81.11.

*4-(4-Methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid, 3,5-bis[2-(aminothioxomethyl)hydrazide] (**2f**)*. Yield: 66 %; m.p. 210 °C; Anal. Calcd. for $C_{18}H_{23}N_7O_3S_2$: C, 48.09; H, 5.16; N, 21.81; S, 14.27 %. Found: C, 48.05; H, 5.19; N, 21.88; S,14.21 %. IR (KBr, cm^{-1}): 3323 (N–H), 3251 (NH–C=O), 3231 (NH_2), 3034 (Ar–H), 1717 (C=O), 1251 (C=S), 1091 (N-C-N), 808 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 9.82 (2H, *s*, NH_2), 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), 181.7 (3,5-C=S), 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); MS (*m*/*z*, (relative abundance, %)): 450.21 (M^++1, 29.12), 331.36, 271.31, 243.25, 215.29, 185.26, 157.21.

*4-[4-(Dimethylaminophenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid, 3,5-bis[2-(aminothioxomethyl)hydrazide] (**2g**)*. Yield: 61 %; m.p. 205 °C; Anal. Calcd. for $C_{19}H_{26}N_8O_2S_2$: C, 49.33; H, 5.67; N, 24.22; S, 13.86 %. Found: C, 49.37; H, 5.69; N, 24.27; S, 13.82 %. IR (KBr, cm^{-1}): 3320 (N–H), 3211 (NH_2), 3118 (NH–C=O), 3021 (Ar–H), 1712 (C=O), 1248 (C=S), 1091 (N––C–N), 812 (Ar–H). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 9.66 (2H, *s*, NH_2), 8.52 (1H, *s*, NH of pyridine ring), 8.03 (1H, *d*, C3–CONH and C5––CONH), 6.62–7.07 (4H, *m*, Ph-ring), 5.13 (2H, *s*, C4–H), 3.06 (1H, *s*, –N(CH_3)$_2$), 2.19 (6H, *s*, C2–CH_3 and C6–CH_3), 2.07 (1H, *d*, NHCS). ^{13}C-NMR (300 MHz, $CDCl_3$, δ / ppm) 112.8, 134.8, 128.3, 148.2, 152.8 (C4 in 4-(CH_3)$_2$N-phenyl ring),

106.3 (3,5-C in pyridine ring), 165.2 (C=O), 181.1 (C=S), 147.9 (2,6-C in pyridine ring), 39.3 (C4 in pyridine ring), 40.8 ($N(CH_3)_2$), 46.5 (C4 in pyridine ring), 18.2 (2,6-CH_3 in pyridine ring). MS (*m*/*z* (relative abundance, %)): 463.22 (M^++1, 16.24), 432.56, 344.41, 284.35, 256.29, 213.23, 199.24, 185.26.

Spectroscopy

The IR spectra of compounds **1a**–**g** 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**–**g** 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**–**g** 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 mass spectral analysis of compounds **1a**–**g** showed molecular ion peaks, which confirmed the molecular mass of these compounds. The IR spectra of compounds **2a**–**g** 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**–**g** 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, NHCS and NH_2 protons resonated as singlets at δ 5.10–5.21, 8.01–8.15, 2.02––2.12 and 9.14–9.82 ppm, respectively. The ^{13}C-NMR spectra of compounds **2a**–**g** 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**–**g** 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**–**g** and **2a**–**g** were screened. The structure activity relationship (SAR) analysis of the base compounds **1a**–**g** was compared with that of the thiosemicarbazone-containing compounds **2a**–**g**. Ciprofloxacin

was used as a standard at 100 μg ml^{-1}. Compounds **1a**–**g** showed low activity compared with compounds **2a**–**g** towards all the tested organisms.

TABLE I. Antibacterial activity of the synthesized compounds **1a**–**g** and **2a**–**g** (disk diameter: 7 cm)

Compound	*S. aureus*	*K. pneumoniae*	*E. coli*	*P. aeruginosa*
1a	–	–	10	14
1b	6	7	5	6
1c	10	–	8	10
1d	–	8	–	–
1e	5	5	6	12
1f	–	6	5	15
1g	5	–	10	6
2a	9	–	16	30
2b	17	18	12	18
2c	25	15	13	10
2d	15	16	25	–
2e	13	12	16	20
2f	11	18	15	22
2g	10	7	18	16
Ciprofloxacin	22	19	27	32

Compounds **2a**–**g** 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 C=S and a 4-chlorophenyl group in the fourth position. On the other hand, compounds **2a**, **2b** and **2d**–**g** had low activities compared with the standard ciprofloxacin.

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

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

Compounds **2a**–**g** were screened for *Pseudomonas aeruginosa*, whereby the compound **2a** exhibited equipotent activity compared with the standard ciprofloxacin, while the other compounds **2b**–**g** had low activities compared with the standard ciprofloxacin.

Antifungal screening

The fungacidal zones of inhibition, mm, values are given in Table II. Compounds **2a**–**g** were screened for *Aspergillus niger*; the compounds **2b**–**g** were less active compared with the standard clotrimazole, while compound **2a** had no activity.

Compounds **2a**–**g** were screened for *Candida albicans*. Compound **2d** was highly active compared with the standard clotrimazole because it contained an amide group in the 3,5-position with C=S and 4-hydroxyphenyl in the fourth position, while the other compounds **2a**–**c** and **2e**–**g** had lower activities than the standard clotrimazole.

TABLE II. Antifungal activity of the synthesized compounds **1a**–**g** and **2a**–**g** (disk diameter: 7 cm)

Compound	*A. niger*	*C. albicans*	*M. audouinii*	*C. neoformans*
1a	–	8	10	–
1b	9	10	8	9
1c	10	16	–	8
1d	14	–	12	–
1e	8	–	–	–
1f	12	15	11	9
1g	5	16	12	–
2a	–	8	6	7
2b	10	–	–	6
2c	15	20	14	13
2d	16	26	18	15
2e	8	11	15	15
2f	16	10	18	24
2g	14	17	16	–
Clotrimazole	22	24	26	25

Compounds **2a**–**g** were screened for *Microsporum audouinii*. The compounds **2a** and **2c**–**g** had lower activity than the standard clotrimazole, while compound **2b** was inactive.

Compounds **2a**–**g** 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 **2g** exhibited no activity.

EXPERIMENTAL

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).

*Synthesis of diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**1a**)*

The reaction mixture consisting of ethyl acetoacetate (0.2 mol), furfural (0.1 mol) and ammonium hydroxide (0.1 mol) in methanol (20 mL) was heated at reflux for 4 h. The ob-

tained solid was filtered off, washed with water and recrystallized using absolute ethanol. The above procedure was followed for the synthesis of compounds **1b**–**g**.

*Synthesis of 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid, 3,5-bis[2-(aminothioxomethyl)hydrazide] (**2a**)*

The reaction mixture consisting of compound **1a** (0.1 mol), thiosemicarbazide (0.2 mol) dissolved in ethanol (30 mL) and a few drops DMSO was heated under reflux for 10 h. The obtained solid was allowed to cool and then poured into crushed ice. The solid was collected by filtration, washed with water and recrystallised using ethanol. The above procedure was followed for the synthesis of compounds **2b**–**g**.

In vitro *antibacterial screening*

The compounds **1a**–**g** and **2a**–**g** were evaluated for their *in vitro* antibacterial activity against *S. aureus* (ATCC-25923), *K. pneumoniae* (recultured), *E. coli* (ATCC-25922) and *P. aeruginosa* (ATCC-27853) by the agar diffusion method[22,23] using Mueller–Hinton agar (Hi--Media) medium. Each compound was tested at a concentration of 100 μg mL^{-1} in DMSO. Ciprofloxacin was used as the standard. The zone of inhibition (mm) was measured after 24 h incubation at 37 ºC.

In vitro *antifungal screening*

The compounds **1a**–**g** and **2a**–**g** were evaluated for their *in vitro* antifungal activity against *A. niger*, *C. albicans*, *M. audouinii* and *C. neoformans* (recultured) using an agar diffusion method[24,25] with Sabouraud's dextrose agar (Hi-Media). Each compound was tested at a concentration of 100 μg mL^{-1} in DMSO. Clotrimazole was used as the standard. The zone of inhibition (mm) was measured after 24 h incubation at 37 °C.

CONCLUSIONS

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

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ИЗВОД

СИНТЕЗА И АНТИМИКРОБНА АКТИВНОСТ НОВЕ СЕРИЈЕ ДЕРИВАТА 1,4-ДИХИДРОПИРИДИНА

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Ханчовом синтезом добијена је нова серија деривата 1,4-дихидропиридина (**1a**–**g**). Једињења **1a**–**g** реаговала су са тиосемикарбазидима и добијена је нова серија једињења **2a**–**g**.

Структура синтетисаних једињења је потврђена ИЦ, 1H-NMR, 13C-NMR и масеним спектрима и елементалном анализом. Синтетисаним једињењима је одређена антибикробна активност.

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