SYNTHESIS AND BIOLOGICAL ACTIVITIES OF NEW TETRAHYDROQUINOLINE AND PYRIMIDINE DERIVATIVES

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A series of new tetrahydroquinoline derivatives **(4a-j)** were prepared by one-pot multicomponent, [4+2] cycloaddition route from 4-aminonaphthalene, aromatic aldehydes and dihydrofurane (DHF) by using $InCl_3$ catalyst under reflux temperature and also, pyrimidine derivatives **(5a-n)** were prepared by the same route from benzimidazole, aromatic aldehydes and maleic anhydride by using piperidine catalyst under ultrasonic irradiations. The synthesized tetrahydroquinoline and pyrimidine derivatives were characterized (IR, ^{1}H NMR, ^{13}C NMR). The synthesized tetrahydroquinoline and pyrimidine derivatives have been evaluated for antimicrobial, anti-tuberculosis and anti-inflammatory activities.

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INTRODUCTION

Now a day, a huge number of a heterocyclic compound discovered through various eco-friendly methods like one-pot multicomponent reaction, ultrasonic irradiations technique or Diels-Alder reactions.[1-3] Tetrahydroquinoline and pyrimidine derivatives are broadly used in medicinal chemistry. They showed a huge number of important biological properties such as antimicrobial,[4-7] antimalarial,[8-10]analgesic,[11] anthelmintic,[12] antitumor,[13] anti-inflammatory,[14] antiviral[15-17]and anticancer[18] activity. Keeping the view of the biological importance of heterocyclic compounds,[19] we studied the biological activity of tetrahydroquinoline[20] pyrimidine,[21] thiazolone,[22] and benzenesulfonamide[23] derivatives.

EXPERIMENTAL

The starting materials and various solvents were commercially available (Sigma-Aldrich and Avra labs). Reaction courses were monitored by TLC on silica gel precoated F254 Merck plates. Developed plates were examined with UV lamps (254 nm). Melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. IR spectra were recorded on an FT-IR (Bruker). ^{1}H NMR spectra were recorded on a 400 MHz Bruker spectrometer and were recorded in DMSO-d_6 solvent ^{13}C NMR spectra were recorded in DMSO-d_6 solvent on a 100 MHz Bruker spectrometer. Chemical shifts are reported as δ ppm units (TMS).

The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

General procedure for synthesis of tetrahydroquinoline derivatives

In around bottom flask, 4-aminonaphthalene (0.1 mol), aromatic aldehyde (0.1 mol), dihydrofurane (DHF) (0.1 mol) and catalyst - $InCl_3$ (20 mol %) in EtOH as solvent (5 mL) were refluxed at for 7 h. The reaction condition was checked by employing TLC technique, using ethyl acetate: hexane (5:5) as solvents. After completing reaction, reaction mixture was cooled at room temperature. For crystallization, 10 mL methanol was added to the reaction mixture and then cooled at 22 °C, following stirring for 20 minutes. Products were filtered using G_1 sintered crucible. Products were recrystallized from ethyl alcohol.

11-(2,5-Dimethoxyphenyl)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline (4a)

Blackish grey crystal, m.p. 215-218 °C. FT-IR (KBr cm^{-1}): 3324 (-NH), 2910 (-CH), 1568 (-C=C- aromatic), 1210 (ether), ^{1}H NMR 400 MHz, DMSO-d_6) 9.96 (s, 1H, D_2O exchangeable -NH), 8.32-7.45 (m, 6H, Ar), 6.9-7.10 (m, 2H,Ar), 6.75 (s, 1H, Ar),4.8 (t, 1H, -CH), 4.38 (d, 1H, -CH), 3.77-3.85 (m, 2H, -CH_2), 3.8-(s, 6H, -CH_3), 2.43 (m, 1H, -CH), 1.1-1.7(m, 2H, CH_2).^{13}C NMR (100 MHz, DMSO-d_6): 189.51, 156.24, 153.76, 151.34, 127.72, 125.26, 124.96, 112.90, 111.70, 111.34, 110.34, 104.37, 93.19, 78.0, 76.0, 56.10, 40.0, 38.0, Mass (m/z): $[M+1]^+$: 361.16

11-(4-Cyanophenyl)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline (4b)

Light yellow crystals, m.p 250-253 °C. FTIR (KBr cm^{-1}): 3372 (-NH), 2965 (-CH), 2183 (-CN), 1559 (-C=C- aromatic), 1215 (ether).^{1}H NMR 400 MHz, DMSO-d_6) δ 10.14 (s, 1H, D_2O exchangeable -NH), 8.33- 7.45(m, 6H,

Ar), 7.64 (d, 2H, Ar), 7.34 (d, 2H, Ar), 4.82 (t, 1H, CH), 4.37 (d, 1H, CH), 3.77-3.85 (m, 2H, CH_2), 2.43 (m, 1H, CH), 1.1-1.7(m, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 188.51, 156.14, 153.71, 150.92, 127.69, 125.36, 125.05, 112.84, 111.66, 118.0, 111.3, 110.41, 104.39, 93.19, 78.0, 76.0, 40.0, 38.0, Mass (m/z): $[M+1]^+$326.13

11-(3-Hydroxy-4-methoxyphenyl)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline (4c)

Brown cystals, m.p. 210-212 °C. FTIR (KBr cm^{-1}): 3377 (-OH), 3338 (-NH), 2940 (-CH), 1556 (-C=C-aromatic), 1213(ether); ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.95 (s, 1H, D_2O exchangeable -NH), 8.32-7.44 (m, 6H, Ar),7.12-6.92 (d, 2H,Ar), 7.02 (s, 1H, Ar, 4.9 (s, 1H,-OH), 4.8 (t, 1H, -CH), 4.39 (d, 1H, -CH), 3.67-3.88 (m, 2H, -CH_2), 3.8 (s, 3H, -CH_3), 2.43 (m, 1H, -CH_2), 1.1-1.8 (m, 2H, -CH_2), ^{13}C NMR (100 MHz, DMSO-d_6): 192.60, 157, 153.98, 152.44, 128.02, 126.26, 125.16, 113.10, 112.20, 111.53, 110.14, 105.01, 93.20, 78.0, 76.0, 56.11, 40.10, 38.0, Mass (m/z): $[M+1]^+$347.15.

11-(Phenyl)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline (4d)

White crystals, m.p. 200-203 °C. FTIR (KBr cm^{-1}): 3357 (-NH), 2922 (-CH), 1578 (-C=C- aromatic), 1216 (ether), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.92 (s, 1H, D_2O exchangeable -NH), 8.32-7.47 (m, 6H,Ar),7.62-7.10 (m, 5H,Ar), 4.8 (t, 1H, -CH), 4.39 (d, 1H, -CH), 3.68-3.86 (m, 2H, -CH_2), 2.42 (m, 1H, -CH_2), 1.1-1.7 (m, 2H, -CH_2), ^{13}C NMR (100 MHz, DMSO-d_6): 191.98, 157.45, 153.97, 153.64, 127.92, 126.23, 125.36, 113.12, 112.20, 111.53, 110.14, 105.25, 92.23, 78.08, 76.11, 40.02, 38.13, Mass (m/z): $[M+1]^+$301.14.

11-(3-Bromophenyl)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline (4e)

Brown crystals, m.p. 195-197°C, FTIR (KBr cm^{-1}): 3372 (-NH), 2930 (-CH), 1581 (-C=C-aromatic), 1237 (ether), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.93 (s, 1H, D_2O exchangeable -NH), 8.33-7.47 (m, 6H, Ar),7.46 (s, 1H, Ar), 7.52-7.26(m, 3H, Ar), 4.8 (t, 1H, -CH), 4.39 (d, 1H, -CH), 3.67-3.88 (m, 1H, -CH), 2.44 (m, 2H, -CH_2), 1.1-1.79 (m, 2H, -CH_2), ^{13}C NMR (100 MHz, DMSO-d_6): 192.63, 148.25, 154.18, 152.10, 127.87, 126.12, 124.96, 114.00, 112.21, 111.62, 110.04, 105.11, 93.31, 78.12, 76.06, 40.25, 38.07, Mass (m/z): $[M+1]^+$381.00.

11-(4-Methoxyphenyl)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline (4f)

Whitecrystals, m.p. 216-218 °C, FTIR (KBr cm^{-1}): 3377 (-NH), 2931 (-CH), 1562 (-C=C- aromatic), 1234 (ether), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.94 (s, 1H, D_2O exchangeable –NH), 8.31-7.43 (m, 6H, Ar),7.23 (d, 2H, Ar), 7.04 (d, 2H, Ar), 4.81 (t, 1H, -CH), 4.40 (d, 1H, -CH), 3.67-3.86 (m, 2H, -CH_2), 3.82 (s, 3H, -CH_3), 2.44 (m, 1H, -CH_2), 1.13-1.80 (m, 2H, -CH_2),^{13}C NMR (100 MHz, DMSO-d_6): 189.63, 157.25, 154.15, 152.54, 128.22, 126.46, 125.12, 113.08, 112.15, 111.51, 111.01, 105.31, 92.96, 78.0.1, 76.22, 56.21, 40.30, 38.06, Mass (m/z): $[M+1]^+$331.16

11-(4-Chlorophenyl)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline (4g)

Olive green crystals,m.p 160-164 °C. FTIR (KBr cm^{-1}): 3382 (-NH), 2917 (-CH), 1563 (-C=C-aromatic), 1209 (ether), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.96 (s, 1H, D_2O exchangeable -NH), 8.31-7.45 (m, 6H, Ar), 7.66 (d, 2H, Ar), 7.52 (d, 2H, Ar), 4.80 (t, 1H, -CH), 4.41 (d, 1H, -CH), 3.67-3.85 (m, 2H, -CH_2), 2.44 (m, 1H, -CH_2), 1.13-1.78 (m, 2H, -CH_2), ^{13}C NMR (100 MHz, DMSO-d_6): 186.41, 148.60, 148.40, 148.11, 139.99, 136.80, 131.14, 129.79, 131.72, 127.02, 126.81, 126.44, 126.57, 123.97, 123.91, 113.30, 93.00, 79.12, 78.00, 40.12, 38.20, Mass (m/z): $[M+1]^+$335.12.

11-(2,4-Dicyanophenyl)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline (4h)

White crystals, m.p. 220-222 °C. FTIR (KBr cm^{-1}): 3384 (-NH), 2932 (-CH), 1545 (-C=C-aromatic), 1218 (ether), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.98 (s, 1H, D_2O exchangeable -NH), 8.32-7.47 (m, 6H, Ar),7.78 (s, 1H, Ar), 7.46 (d, 1H, Ar), 7.11 (d, 1H, Ar), 4.82 (t, 1H, -CH), 4.40 (d, 1H, -CH), 3.67-3.86 (m, 2H, -CH_2), 2.45 (m, 1H, -CH_2), 1.14-1.79 (m, 2H, -CH_2), ^{13}C NMR (100 MHz, DMSO-d_6): 190.61, 156.00, 153.88, 12.44, 127.92, 126.16, 125.10, 113.13, 112.21, 121.93, 110.09, 105.11, 93.19, 78.05, 76.11, 40.22, 38.12, Mass (m/z): $[M+1]^+$369.07.

11-(4-Nitrophenyl)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline(4i)-

Yellow crystals, m.p 222-223 °C, FTIR (KBr cm^{-1}): 3300 (-NH), 2921 (-CH), 1550 (-C=C-aromatic), 1217 (ether), ^{1}H NMR 400 MHz, DMSO-d_6) δ 10.00 (s, 1H, D_2O exchangeable -NH), 8.77-7.10 (m, 6H,Ar),8.11 (d, 2H, Ar), 7.61 (d, 2H, Ar), 4.80 (t, 1H, -CH), 4.37 (d, 1H, -CH), 3.68-3.33 (m, 2H, -CH_2), 2.44 (m, 1H, -CH_2), 1.1-1.45 (m, 2H, -CH_2), ^{13}C NMR (100 MHz, DMSO-d_6): 187.51, 158.69, 149.30, 147.51, 141.90, 133.90, 130.04, 128.89, 127.92, 126.96, 126.80, 126.34, 126.25, 124.17, 123.81, 113.20, 93.00, 79.10, 78.00, 40.02, 38.23,Mass (m/z): $[M+1]^+$346.15.

11-(4-Flurophenyl)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline (4j)

White crystals, m.p 211-213 °C. FTIR (KBr cm^{-1}): 3321 (-NH), 2920 (-CH), 1536 (-C=C-aromatic), 1205 (ether), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.94 (s, 1H, D_2O exchangeable -NH), 8.31-7.44 (m, 6H, Ar),7.32 (d, 2H, Ar), 7.21 (d, 2H, Ar), 4.80 (t, 1H, -CH), 4.39 (d, 1H, -CH), 3.66-3.80 (m, 2H, -CH_2), 2.43 (m, 1H, -CH_2), 1.13-1.70 (m, 2H, -CH_2), ^{13}C NMR (100 MHz, DMSO-d_6): 179.21, 152.49, 148.30, 147.33, 141.84, 133.72, 131.14, 127.89, 127.88, 127.16, 126.65, 126.96, 125.83, 124.10, 123.41, 113.90, 92.90, 78.93, 78.00, 40.00, 38.13,Mass (m/z): $[M+1]^+$319.14.

General procedure for pyrimidine derivatives

In the ultrasound-assisted method, a mixture of piperidine (10 mol %), isoniazide (0.1 mol), aldehyde (0.1 mol) and maleic anhydride (0.1 mol) in dichloroethane (DCE) as solvent (5 mL) was irradiated with ultrasound (with a frequency of 50 Hz and power of 250 V AC) at 70 °C for 2 h. The reaction progress was checked on TLC using ethyl acetate:hexane (5:5) as solvents. After the completion of reaction, the mixture was cooled at room temperature. Charged methanol (10 mL) was used for crystallization and then the mixture was cooled to 22 °C and stirred for 30 min. The product was filzterd with G_1 sintered crucible and recrystallized from ethyl alcohol.

4-(4-Methoxyphenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-a]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5a)

White crystals, m.p. 250-252 °C. FTIR (KBr cm^{-1}): 3250 (-NH), 2803 (-CH), 1727 (C=O), 1612 (C=N), 1660 (C=C aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.8 (s, 1H, D_2O exchangeable NH), 6.13-7.95 (m, 8H, Ar), 3.86 (s, 1H, -CH), 3.1-3.2 (s, 3H, -CH_3), 2.6 (d, 1H, -CH), 2.3 (d, 1H, -CH), ^{13}C NMR (100 MHz, DMSO-d_6): 168.27, 168.12, 166.49, 151.40, 149.09, 137.05, 132.72, 130.22, 129.66, 129.51, 129.09, 123.10, 121.14, 113.76, 112.03, 80.13, 57.0, 47.10, 40.0-39.1, Mass (m/z): $[M + 1]^+$349.12.

4-(2,5-Dimethoxyphenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]-furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5b)

White crystals, m.p. 168-170 °C. FTIR (KBr cm^{-1}): 3249 (-NH), 2826 (-CH), 1723 (C=O), 1618 (-C=N), 1568 (C=C aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.86 (s, 1H, D_2O exchangeable NH), 6.16-7.97 (m, 7H, Ar), 3.82 (s, 1H -CH), 3.2 (d, 1H, -CH), 2.7 (s, 6H, 2-CH_3), 2.4 (d, 1H, -CH), ^{13}C NMR (100 MHz, DMSO-d_6): 170.00, 169.02, 160.19, 151.45, 150.09, 139.15, 132.13, 131.32, 130.22, 130.04, 129.96,a 129.74, 129.09, 123.09, 121.94, 113.76, 111.57, 79.0, 56.90, 46.97, 38.91- 40.0, Mass (m/z): $[M+1]^+$379.12.

4-(3,4-Dihydroxyphenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5c)

White crystals, m.p. 223-225 °C. FTIR (KBr cm^{-1}): 3282 (-OH), 3239 (-NH), 2825 (-CH), 1731 (-C=O), 1620 (-C=N), 1587 (C=C aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.8 (s, 1H, D_2O exchangeable NH), 6.38-7.95 (m, 7H, Ar), 4.82 (s, 2H, CH_2), 3.1 (m, 1H, CH), 2.6 (d, 1H, CH), 2.3 (d, 1H, CH), ^{13}C NMR (100 MHz, DMSO-d_6): 170.10, 168.53, 165.19, 151.61, 148.84, 142.56, 136.01, 130.85, 122.79, 120.94, 118.76, 116.45, 117.35, 114.98, 111.52, 101.12, 79.0, 44.53,Mass (m/z): $[M+1]^+$351.09.

4-(3-Hydroxyphenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5d)

White crystals, m.p.201-202 °C. FTIR (KBr cm^{-1}): 3278 (-OH), 3229 (-NH), 2839 (-CH), 1722 (-C=O), 1628 (C=N), 1568 (-C=C-aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.87 (s, 1H, D_2O exchangeable NH), 6.68-7.71 (m, 8H,Ar), 4.82 (s, 1H,-OH), 3.82 (s, 1H, -CH), 3.2 (d, 1H, -CH), 2.4 (d, 1H, -CH), ^{13}C NMR (100 MHz, DMSO-d_6): 170.30, 169.12, 165.00, 157.19, 141.35, 140.29, 138.14, 135.15, 133.13, 131.32, 130.04, 129.09, 121.94, 120.21, 119.23, 118.34, 118.12, 115.41, 114.76, 111.57, 96.5, 75.0, 40.0,Mass (m/z): $[M+1]^+$335.08.

4-(4-Cyanophenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5e)

Yellow crystals, m.p. 194-196 °C. FTIR (KBr cm^{-1}): 3262 (-NH), 2845 (-CH), 2184 (-CN), 1727 (-C=O), 1618 (C=N aromatic), 1577 (-C=C-aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.9(s, 1H, D_2O exchangeable NH), 6.16-8.00 (m, 8H,Ar), 3.93 (s, 1H, -CH), 3.2 (d, 1H, -CH), 2.4 (d, 1H, -CH), ^{13}C NMR (100 MHz, DMSO): 170.50, 168.52, 164.19, 151.45, 142.23, 139.75, 132.13, 131.92, 130.02, 129.66, 129.74, 129.09, 119.09, 118.94, 118.56, 113.76, 115.08, 111.07, 102.00, 77.10, 41.97,Mass (m/z): $[M+1]^+$344.09.

4-(3-Hydroxy,4-methoxyphenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5f)

Yellow crystals, m.p. 210-212 °C. FTIR (KBr cm^{-1}): 3289 (-OH), 3239 (-NH), 2819 (-CH), 1741 (-C=O), 1612 (C=N), 1582 (C=C aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.88 (s, 1H, D_2O exchangeable NH), 6.31-7.46 (m, 7H, Ar), 4.15 (s, 1H, -OH), 3.91 (s, 1H, -CH), 3.2 (d, 1H, -CH), 3.0 (s, 3H, -CH_3), 2.2 (d, 1H, -CH), ^{13}C NMR (100 MHz, DMSO-d_6): 170.20, 168.32, 163.19, 151.85, 148.09, 142.32, 138.35, 133.13, 121.94, 119.54, 118.21, 115.30, 112.35, 111.17, 76.0, 56.90, 42.17, Mass (m/z): $[M + 1]^+$365.09

4-(Phenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5g)

White crystals, m.p. 245-248 °C. FTIR (KBr cm^{-1}): 3250 (-NH), 2812 (-CH), 1717 (-C=O), 1620 (C=N), 1592 (-C=C-aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.94 (s, 1H, D_2O exchangeable NH), 6.08-7.97 (m, 9H, Ar), 3.76 (s, 1H, -CH), 3.17 (d, 1H, -CH), 2.54 (d, 1H, -CH),^{13}C NMR (100 MHz, DMSO-d_6): 170.35, 168.52, 164.75, 151.95, 147.46, 138.37, 132.12, 131.13, 130.65, 129.71, 129.57, 129.22, 128.29, 122.80, 121.60, 114.21, 111.54, 79.0, 46.97, 38.9, 40.10**,** Mass (m/z): $[M+1]^+$319.11.

4-(3-Bromophenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-a]furo[3,4-*e*]pyrimidine 1,3(3a*H*,11a*H*)-dione (5h)

Brown crystals, m.p. 238-240 °C. FTIR (KBr cm^{-1}): 3259 (-NH), 2829 (-CH), 1719 (-C=O), 1628 (C=N), 1584 (-C=C-aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.8 (s, 1H, D_2O exchangeable NH), 6.20-7.86 (m, 8H, Ar), 3.90 (s, 1H,-CH), 3.1 (d, 1H, -CH), 2.4 (d, 1H, -CH), ^{13}C NMR (100 MHz, DMSO-d_6): 170.25, 168.02, 163.19, 142.22, 142.09, 133.20, 130.14, 126.96, 126.12, 123.19, 119.02, 118.14, 115.46, 111.07, 99.65, 76.0, 41.68,Mass (m/z): $[M+1]^+$397.01

4-(4-Hydroxyphenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine 1,3(3a*H*,11a*H*)-dione (5i)

White crystals, m.p. 190-192 °C. FTIR (KBr cm^{-1}): 3279 (-OH), 3243 (-NH), 2829 (-CH), 1713 (C=O), 1621 (C=N), 1588 (-C=C-aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.83 (s, 1H, D_2O exchangeable NH), 6.20-7.91 (m, 8H, Ar), 3.93 (s, 1H, -OH), 3.78 (s, 1H, -CH), 2.9 (d, 1H, -CH), 2.43 (d, 1H, -CH), ^{13}C NMR (100 MHz, DMSO-d_6): 170.50, 168.22, 163.69, 160.00, 142.65, 140.11, 139.05, 130.00, 130.04, 129.19, 119.09, 118.94, 115.66, 111.47, 75.0, 99.90, 41.97, Mass (m/z): $[M+1]^+$335.08.

4-(4-Chlorophenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine 1,3(3a*H*,11a*H*)-dione (5j)

White crystal, m.p. 215-218 °C. FTIR (KBr cm^{-1}): 3268 (-NH), 2855 (-CH), 1717 (-C=O), 1630 (-C=N), 1576 (C=C aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.95 (s, 1H, D_2O exchangeable NH), 6.14-7.92 (m, 8H,Ar), 3.8 (s, 1H, -CH), 3.2-3.0 (d, 1H, -CH), 2.5 (d, 1H, -CH),^{13}C NMR (100 MHz, DMSO-d_6): 170.35, 168.78, 164.60, 151.66, 147.46, 136.02, 131.16, 131.03, 130.02, 129.82, 129.60, 128.92, 128.42, 123.01, 121.45, 113.79, 111.42, 79.0, 44.40, 38.0-40.00,Mass (m/z): $[M+1]^+$353.00.

4-(2,4-Dichlorophenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5k)

Brownish crystals, m.p. 180-184 °C. FTIR (KBr cm^{-1}): 3168, 2665, 2130, 1658, 1615, 1591, 1536; ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.90 (s, 1H, D_2O exchangeable NH), 6.23-7.9 (m, 7H, Ar), 3.7 (s, 1H), 3.2-3.2 (d, 1H), 2.5 (d, 1H), ^{13}C NMR (100 MHz, DMSO-d_6): 170.30, 168.68, 163.90, 151.56, 146.40, 135.02, 131.26, 131.23, 131.02, 129.72, 129.60, 128.49, 128.43, 123.11, 121.53, 114.89, 112.00, 79.00, 44.35, 38.0-40.05,Mass (m/z): $[M+1]^+$387.02.

4-(4-Nitrophenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5l)

Yellow crystals, m.p. 210-212 °C. FTIR (KBr cm^{-1}): 3261 (-NH), 2831 (-CH), 1734 (-C=O), 1735 (C=N), 1572 (C=C aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.9 (s, 1H, D_2O exchangeable NH), 6.16-8.40 (m, 8H, Ar), 3.82 (s, 1H, -CH), 3.3 (d, 1H, -CH), 2.3 (d, 1H, -CH), ^{13}C NMR (100 MHz, DMSO-d_6): 170.30, 168.12, 164.19, 151.05, 142.25, 139.05, 137.13, 127.49, 127.90, 129.54, 118.76, 115.23, 111.07, 76.0, 41.04, Mass (m/z): $[M+1]^+$364.09.

4-(4-Fluorophenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5m)

Greenish crystals, m.p. 220-222 °C. FTIR (KBr cm^{-1}): 3246 (-NH), 2802 (-CH), 1710 (-C=O), 1630 (-C=N) 1594 (C=C aromatic),^{1}H NMR 400 MHz, DMSO-d_6) δ 9.0 (s, 1H, D_2O exchangeable NH), 6.10-7.95 (m, 8H, Ar), 3.7 (s, 1H, -CH), 3.2-3.0 (d, 1H, -CH), 2.5 (d, 1H, -CH), ^{13}C NMR (100 MHz, DMSO-d_6): 170.20, 168.53, 164.30, 151.61, 148.00, 138.00, 136.14, 131.00, 122.97, 122.00, 114.00, 111.52, 79.00, 44.53, 39.00-40.00,Mass (m/z): $[M + 1]^+$337.08.

4-(2,3-Dihydroxyphenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione (5n)

Milky white crystals, m.p. 198-200 °C. FTIR (KBr cm^{-1}): 3266 (-OH), 3225 (-NH), 2869 (-CH), 1725 (-C=O), 1624 (-C=N), 1542 (-C=C- aromatic), ^{1}H NMR 400 MHz, DMSO-d_6) δ 9.88 (s, 1H, D_2O exchangeable NH), 6.16-7.68 (m, 7H, Ar), 4.7(s, 2H, -OH), 3.82 (s, 1H, -CH), 3.0 (d, 1H,-CH), 2.4 (d, 1H, -CH), ^{13}C NMR (100 MHz, DMSO-d_6): 169.90, 169.02, 160.25, 151.45, 150.29, 149.15, 132.43, 131.32, 130.02, 130.04, 129.96, 129.74, 129.09, 123.09, 121.94, 113.76, 111.77, 101.00, 78.00,41.00., Mass (m/z): $[M+1]^+$351.08.

Biological activity

The in-vitro antimicrobial activity has been studied by a disc diffusion method or Kirby-Bauer method[24] with different strains of bacteria and fungi. Gentamicin and amphotericin B were used as positive controls for bacteria and fungi, respectively. The compounds were screened for antibacterial activity against *E. coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Staphylococcusaureus*ATCC 25923 in Mueller-Hinton agar (M173) medium, and for antifungal activity against *Candida sp.* in Sabouraud‘s dextrose agar medium. The plates were incubated at 37 °C for 24 h for both antibacterial and antifungal activities.

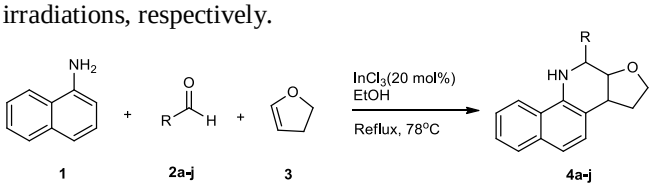
The in-vitro antituberculosis activity has been carried out by CLAIRO COMBI method[25]with tuberculosis bacteria and Streptomycin was used as a positive control. Liquefied sterile Lowenstein-Jensen agar is poured into Petri dishes kept on the level surface. Media depth was 4 mm. After solidification, the dishes were dried for 30 min in an incubator at 37 °C to remove excess moisture from the surface. While pouring into the plates, 5 % defibrinated sterile blood was added to the test organism. The plates were incubated at 37 °C for 4 days.

In vitro anti-inflammatory activity measurement (human red-blood-cell (HRBC) membrane stabilization method): Fresh whole human blood (5mL) are collected and transferred to the centrifuged tubes containing Heparin or EDTA or sodium citrate to prevent clotting. The tubes are centrifuged at 3000 rpm for 10 min and are washed three times with equal volume of normal saline. The volume of the blood is measured and reconstituted as 10% v/v suspension with normal saline. The reaction mixture consists of 1.0mL of a test sample of different concentrations in normal saline and 0.5mL of 10% HRBC suspension, 1 mL of 0.2 M phosphate buffer, 1 ml hypo saline were incubated at 37°C for 30 min and centrifuged at 3,000 rpm for 30 mins. The hemoglobin content of the supernatant solution was estimated spectrophotometrically at 560 nm. Diclofenac was used as a control.[26-29]

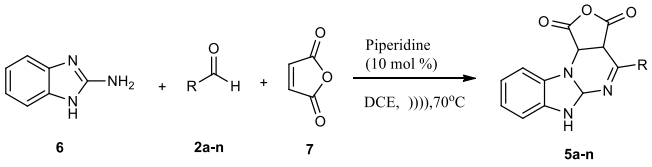
RESULTS AND DISCUSSION

We have synthesized (11-(*R*)-2,3,3a,10,11,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinoline(**4a-j**) (Scheme 1 and Table 1) and 4-(*R*)-5a,6-dicyclobenzo[4,5]imidazo[1,2-*a*]furo[3,4-*e*]pyrimidine-1,3(3a*H*,11a*H*)-dione derivatives

(**5a-n**) (Scheme 2 and Table 2) via one-pot multi-component [4+2]cycloaddition reactions of dienes and a dienophiles using $InCl_3$ or piperidine as Lewis base catalyst in EtOH under reflux or in dichloroethane under ultrasound irradiations, respectively.



Scheme 1. Synthesis of tetrahydroquinoline derivatives.



Scheme 2. Synthesis of pyrimidine derivatives

First, imines (Schiff bases) form from the 4-aminonaphthalene (**1**) or 2-aminobenzimidazole (**6**) and the aromatic aldehydes (**2a-j**) and these are cyclized with dihydrofurane (**3**) or maleic anhydride (**7**) into the appropriate condensed heterocycles (**6** and **7**, respectively). The synthesized tetrahydroquinoline (**4a-j**) and pyrimidine (5**a-n**) derivatives were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy techniques.

The prepared compounds have been screened for antibacterial, antifungal, antituberculosis[32] and anti-inflammatory activities and measured the zones showing complete inhabitation and record the diameters of zones to the nearest millimeter. The results are summarized in Tables 3 and 4.

All tetrahydroquinoline derivatives (**4a-j**) showed antibacterial activity only against *Staphylococcus aureus* ATCC 25923 bacteria but did not show any activity against *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC27853 or antifungal activity against *Candida sp.*

Table 1. Tetrahydroquinoline derivatives synthesized using $InCl_3$ as catalyst via [4+2] cycloaddition route

Entry	R	Product	Time, h	Yield, %	M.p.,^{o}C
1	2,5-$(MeO)_2C_6H_3$	**4a**	3.15	88	218
2	4-CNC_6H_4	**4b**	3.50	81	253
3	4-HO-3-$MeOC_6H_3$	**4c**	3.40	77	212
4	Ph	**4d**	2.45	80	203
5	3-BrC_6H_4	**4e**	3.20	81	197
6	4-$MeOC_6H_4$	**4f**	3.48	80	218
7	4-ClC_6H_4	**4g**	3.30	79	164
8	2,4-$(Cl)_2C_6H_3$	**4h**	4.00	76	222
9	4-$NO_2C_6H_4$	**4i**	2.15	74	223
10	4-FC_6H_4	**4j**	3.27	82	213

Table 2. Pyrimidine derivatives synthesized using piperidine as catalyst via [4+2] cycloaddition route

Entry	R	Product	Time, min	Yield, %	M.P.,^{o}C
1	4-$MeOC_6H_4$	**5a**	68	80	252
2	2,5- $MeO_2C_6H_3$	**5b**	30	74	170
3	3,4-$HO_2C_6H_3$	**5c**	60	77	225
4	3-HOC_6H_4	**5d**	32	78	202
5	4-CNC_6H_4	**5e**	52	73	196
6	4-HO-3-$MeOC_6H_3$	**5f**	48	71	212
7	Ph	**5g**	53	75	248
8	3-BrC_6H_4	**5h**	63	79	240
9	4-HOC_6H_4	**5i**	72	69	192
10	4-ClC_6H_4	**5j**	69	78	218
11	2,4-$Cl_2C_6H_3$	**5k**	74	76	184
12	4-$NO_2C_6H_4$	**5l**	64	71	212
13	4-FC_6H_4	**5m**	79	77	222
14	2,3-$HO_2C_6H_3$	**5n**	50	74	200

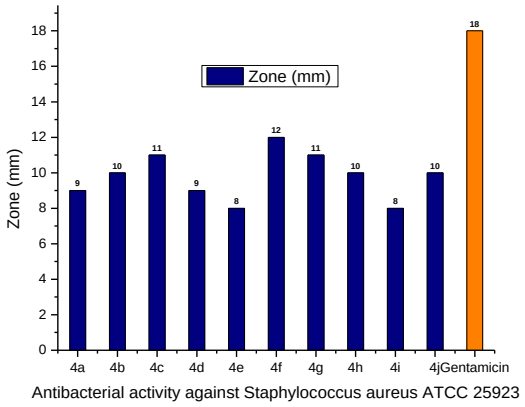


Figure 1. Anti-bacterial activity of tetrahydroquinoline derivatives against *Staphylococcus aureus* ATCC 25923

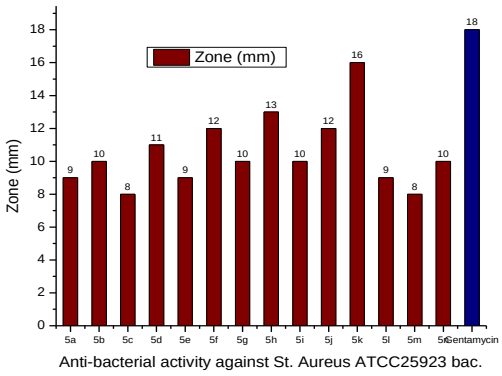


Figure 2. Anti-bacterial activity of pyrimidine derivatives against *Staphylococcus aureus* ATCC 25923

All pyrimidine derivatives (**5a-n**) showed antibacterial activity only against *Staphylococcus aureus* ATCC 25923 bacteria, but not showed against *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC27853. Two pyrimidine derivatives samples (**5j** and **5k**) showed antifungal activity against *Candida sp.*

Antituberculosis activity

The tetrahydroquinoline derivatives (**4a-j**) do not show any antituberculosis activity, but all pyrimidine derivatives (**5a-n**) hadantituberculosisactivity. The compound **5k** showed activity in the higher while **5a, 5h** and **5i** in the lower zone.

The percentage of HRBC hemolysis and membrane stabilization or protection was calculated by using the standard formula.

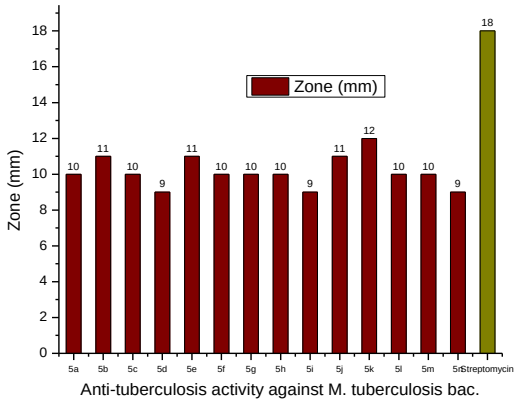


Figure 3. The anti-tuberculosis activity of pyrimidine derivatives

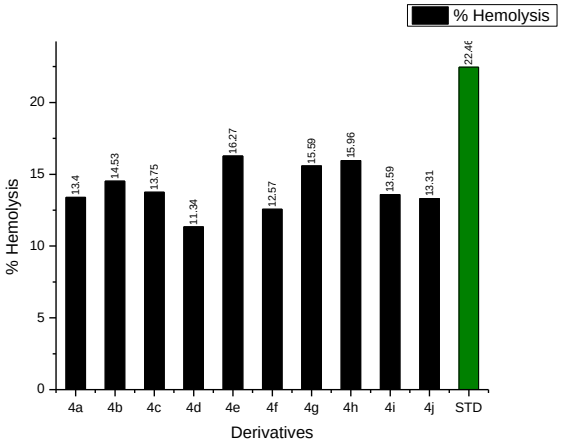


Figure 4. Anti-inflammatory activity of tetrahydroquinoline derivatives

The results can be seen in Tables **3** and **4.** In the tetrahydroquinoline-series, sample (**4d**) showed the highest percentage of HRBC membrane stabilization and sample (**4h**) showed the lowest rate of HRBC membrane stabilization.

In pyrimidine derivatives case, sample (**5a**) showed the highest percentage of HRBC membrane stabilization and sample (**5c**) showed the lowest rate of HRBC membrane stabilization.

Table 3. Anti-inflammatory activity of tetrahydroquinoline derivatives (**4a-j**)

Product	% Hemolysis	% Protection	Product	% Hemolysis	% Protection
4a	13.40	86.59	**4g**	15.59	84.40
4b	14.53	85.46	**4h**	15.96	84.03
4c	13.75	86.24	**4i**	13.59	86.40
4d	11.34	88.65	**4j**	13.31	86.68
4e	16.27	83.72	**Ref.**	22.46	77.53
4f	12.57	87.42			

Table 4. Anti-inflammatory activity of pyrimidine derivatives (**5a-5n**)

Product	% Hemolysis	% Protection	Product	% Hemolysis	% Protection
5a	15.52	84.47	**5h**	16.03	83.96
5b	18.07	81.92	**5i**	16.38	83.61
5c	20.94	79.07	**5j**	17.62	82.37
5d	19.67	80.32	**5k**	17.74	82.25
5e	17.35	82.62	**5l**	16.87	83.12
5f	17.48	82.51	**5m**	20.18	79.81
5g	19.02	80.97	**5n**	19.11	80.88
			Ref.	22.46	77.53

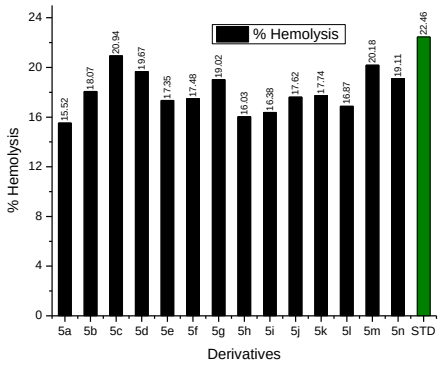


Figure 5. Anti-inflammatory activity of pyrimidine derivatives (**5a-5n**)

CONCLUSION

We have used an eco-friendly route for the preparation of new tetrahydroquinoline and pyrimidine derivatives and screened for their antibacterial against *E. coli, Pseudomonas aeruginosa and Staphylococcus aureus*, antifungal activity against *Candida sp.*, anti-tuberculosis activity against *tuberculosis bacteria* and in vitro anti-inflammatory activity. We have concluded that these series of compounds certainly hold great promise toward good active leads in medicinal chemistry.

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