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Synthesis of new 4-aryl-3, 4-dihydropyrimidin-2(*1H*)-ones/ thiones/ imines and their antimicrobial evaluation

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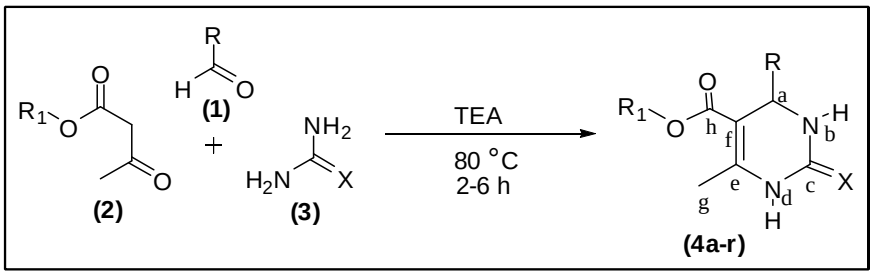
ABSTRACT

A series of new 4-aryl-3, 4-dihydropyrimidin-2(*1H*)-ones/ thiones/ imine derivatives (**4a-r**) have been synthesized by an environment friendly methodology. Their chemical structures were confirmed by means of IR, ^{1}H and ^{13}C NMR Spectroscopic techniques, mass spectometry and elemental analysis. Further they had subjected for the antimicrobial activity evaluation and they exhibited significant activity.



Keywords: 4-Aryl-3, 4-dihydropyrimidin-2(*1H*)-ones/ thiones/ imines, triethylamine, antimicrobial activity.

INTRODUCTION

The 4-aryl-3, 4-dihydropyrimidin-2(*1H*) ones/ thiones/ imines are an important class of compounds exhibiting broad spectra of pharmacological activities such as anti-microbial and antihypertensives[1-2]. These compounds have a huge interest in the medicinal chemistry community in recent years.

Moreover, this class of heterocycles revealed other pharmacological activities such as anti-inflammatory,[3] calcium channel modulators,[4] antifungal anti bacterial,[5] melanin concentrating hormone receptor (MCHI-R) antagonists,[6] chemical modulators of heat shock protein 70 (Hsp 70),[7] hepatitis B replication inhibitors[8] and inhibitors of the fatty acid transporters.[9] This set of potentialities linked to the possibility of chemical modulation in all positions of the dihydropyrimidineone/ thione/ imines rings make dihydropyrimidines a privileged structure, justifying the great interest in their synthesis.

In this study, synthesis, structural elucidation and antimicrobial evaluation of a new series of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones/ thiones/ imines derivatives having 4-diethyl amino-3-hydroxy, 4- pyrrolidin-1-yl and 4-tetrahydro-*2H*- pyron-4-yl at position 4 in phenyl ring are reported.

EXPERIMENTAL SECTION

2.1. General

Chemicals were procured from Sigma-Aldrich, Merck and Lancaster, used as such without further purification. All solvents used for the spectroscopic and other physical studies were reagent grade and further purified by literature methods.[10] Melting points were determined in open capillary tubes on a Mel-temp apparatus and were uncorrected. Micro analysis was performed at University of Hyderabad, Hyderabad. IR Spectra were recorded in Environmental Engineering Lab, S.V.University, Tirupati as KBr discs on a Nicolet 380 FT-IR spectrophotometer and absorptions were reported in wave numbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded as solutions in DMSO-d_6 on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C. The ^1H and ^{13}C NMR chemical shifts were referenced to tetramethylsilane (TMS). Mass spectra were recorded on a Jeol SX 102 DA/ 600 mass spectrometer using Argon / Xenon (6 keV, 10 mA) as the FAB gas.

2.2. Chemistry

2.2.1. Synthesis

Ethyl-4-(4-diethylamino)-3-hydroxyphenyl)-6-methyl-2oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4a)

A mixture of 4-(diethyl amino)-3-hydroxybenzaldehyde (0.290 g, 1.5 mmol), ethyl acetoacetate (0.195 g, 1.5 mol), urea (0.120 g, 2.0 mol) and triethylamine (catalytic amount) was heated at 80 °C for 3h. The progress of the reaction was monitored by TLC analysis. After completion of reaction, cooled the reaction mixture and then poured into crushed ice with stirring. The solid was filtered and purified by recrystallisation from ethanol to give analytically pure product 0.41 g (80 %), mp 143-145 ºC. The same procedure was adopted for the preparation of other compounds **4b-r**.

2.2.2. Spectral and elemental analysis of the synthesized compounds.

2.2.2.1.Ethyl-4-(4-(diethylamino)-2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4a): Solid; mp 143-145 ºC; IR (cm^{-1}): ν_{max} 3594 (OH), 3487-3410 (NH), 1655 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 10.36 (brs, 1H, H-d), 10.06 (brs, 1H, H-b), 9.45 (brs, 1H, OH), 6.96 (d, J = 7.21 Hz, 1H, H-6), 6.26 (d, J = 5.1 Hz, 1H, H-5), 6.14 (s, 1H, H-3), 5.62 (d, J = 6.46 Hz, 1H, H-a), 4.32 (q, J = 6.82 Hz, 2H, CH_2), 3.52 (q, J = 6.42 Hz, 4H, H-7 & H-7'), 2.42 (s, 3H, H-g), 1.29 (t, J = 7.14 Hz, 3H, CH_3), 1.23 (t, J = 6.19 Hz, 6H, H-8 & H-8'); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.5 (C-h), 156.8 (C-2), 151.6 (C-c), 150.3 (C-4), 149.8 (C-e), 129.9 (C-6), 113.3 (C-1), 108.8 (C-f), 106.6 (C-5), 99.3 (C-3), 62.3 ($\underline{C}H_2$), 49.2 (C-a), 48.1 (C-7 & C-7'), 18.9 (C-g), 15.3 ($\underline{C}H_3$), 13.6 (C-8 & C-8'); MS *m/z* (%): 347.18 (29.20), 248.19 (18.90), 169.19 (27.78), 108.18 (61.12), 45.18 (56.12), 29.36 (31.14), 15.18 (21.13); Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10; Found: C, 62.15; H, 7.24; N, 12.08.

2.2.2.2.Ethyl-4-(4-(diethylamino)-2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4b): Solid; mp: 168-170 ºC; IR (cm^{-1}): ν_{max} 3600 (OH), 3502-3415 (NH), 754 (C=S); ^1H NMR (400 MHz, DMSO-d_6) δ: 10.19 (brs,1H, H-d), 10.01 (brs, 1H, H-b), 9.51 (brs, 1H, -OH), 6.92 (d, J = 7.28 Hz, 1H, H-6), 6.27 (d, J = 5.1 Hz, 1H, H-5), 6.12 (s, 1H, H-3), 5.60 (d, J = 6.50 Hz, 1H, H-a), 4.34 (q, J = 6.81 Hz, 2H, CH_2), 3.53 (q, J = 6.45 Hz, 4H, H-7 & H-7'), 2.41 (s, 3H, H-g), 1.28 (t, J = 7.12 Hz, 3H, CH_3), 1.25 (t, J = 6.19 Hz, 6H, H-8 & H-8'); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.8 (C-h), 156.4 (C-2), 151.2 (C-c), 150.4 (C-4), 149.5 (C-e), 129.6 (C-6), 113.4 (C-1), 107.9 (C-f), 106.8 (C-5), 99.5 (C-3), 62.3 ($\underline{C}H_2$), 49.4 (C-a), 48.3 (C-7 & C-7'), 18.7 (C-g), 15.1 ($\underline{C}H_3$), 13.7 (C-8 & C-8'); MS *m/z* (%): 363.16 (100.0), 347.18 (47.22), 248.36 (19.90), 201.46 (47.99), 169.12 (36.87), 102.76 (19.14), 31.18 (33.12), 15.18 (28.86); Anal. Calcd for $C_{18}H_{25}N_3O_3S$: C, 59.48; H, 6.93; N, 11.56; Found: C, 59.41; H, 6.90; N, 11.51.

2.2.2.3.Ethyl-4-(4-(diethylamino)-2-hydroxyphenyl)-2-imino-6-methyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4c): Solid; mp: 180-182 ºC; IR (cm^{-1}): ν_{max} 3591 (OH), 3509-3418 (NH), 1617 (C=N); ^1H NMR (400 MHz, DMSO-d_6) δ: 10.54 (s, 1H, NH), 10.32 (brs, 1H, H-d), 10.02 (brs, 1H, H-b), 9.42 (brs, 1H, -OH), 6.98 (d, J = 7.28 Hz, 1H, H-6), 6.24 (d, J = 5.16 Hz, 1H, H-5), 6.12 (s, 1H, H-3), 5.61 (d, J = 6.48 Hz, 1H, H-a), 4.34 (q, J = 6.80 Hz, 2H, -CH_2), 3.51 (q, J = 6.48 Hz, 4H, H-7 & H-7'), 2.45 (s, 3H, H-g), 1.27 (t, J = 7.18 Hz, 3H,-CH_3), 1.24 (t, J = 6.80 Hz, 6H, H-8 & H-8'); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.7 (C-h), 156.7 (C-2), 152.3 (C-c), 150.3 (C-4), 149.4 (C-e), 129.7 (C-6), 113.8 (C-1), 107.3 (C-f), 106.5 (C-5), 99.3 (C-3), 62.4 ($\underline{C}H_2$), 49.4 (C-a), 48.5 (C-7 & C-7'), 18.3 (C-g), 15.2 ($\underline{C}H_3$), 13.3 (C-8 & C-8'); MS *m/z* (%): 346.20 (19.07), 347.18 (29.20), 248.16 (24.18), 212.13 (100.0), 165.18 (56.88), 104.36 (69.25), 45.13 (33.17), 29.12 (21.22), 15.13 (19.53); Anal. Calcd for $C_{18}H_{26}N_4O_3$: C, 62.41; H, 7.56; N, 16.17; Found: C, 62.32; H, 7.51; N, 16.12;

2.2.2.4.Methyl-4-(4-(diethylamino)-2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4d): Solid; mp 152-154 ºC; IR (cm^{-1}): ν_{max} 3601 (OH), 3579-3440 (NH), 1653 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 10.37 (brs, 1H, H-d), 10.09 (brs, 1H, H-b), 9.51 (brs, 1H, -OH), 6.93 (d, J = 7.28 Hz, 1H, H-6), 6.24 (d, J = 5.16 Hz, 1H, H-5), 6.15 (s, 1H, H-3), 5.66 (d, J = 6.52 Hz, 1H, H-a), 3.54 (q, J = 6.44 Hz, 4H, H-7 & H-7'), 3.28 (s, 3H,-CH_3), 2.40

(s, 3H, H-g), 1.29 (t, *J* = 6.30 Hz, 6H, H-8 & H-8'); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.4 (C-h), 156.3 (C-2), 151.9 (C-c), 150.1 (C-4), 148.9 (C-e), 129.5 (C-6), 113.7 (C-1), 107.7 (C-f), 106.3 (C-5), 99.4 (C-3), 55.4 ($\underline{C}H_3$), 48.3 (C-7 & C-7'), 49.2 (C-a), 18.5 (C-g), 13.4 (C-8 & C-8'); MS *m/z* (%): 333.17 (32.03), 345.10 (23.80), 237.79 (100.0), 169.19 (49.69), 108.38 (64.28), 31.16 (38.76), 15.10 (22.17); Anal. Calcd for $C_{17}H_{23}N_3O_4$: C, 61.25; H, 6.95; N, 12.60; Found: C, 61.20; H, 6.92; N, 12.55.

2.2.2.5.Methyl-4-(4-(diethylamino)-2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4e): Solid; mp: 148-150 ºC; IR (cm^{-1}): ν_{max} 3592 (OH), 3502-3417 (NH), 758 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.37 (brs,1H, H-d), 10.03 (brs, 1H, H-b), 9.47 (brs, 1H, -OH), 6.98 (d, *J* = 7.28 Hz, 1H, H-6), 6.29 (d, *J* = 5.18 Hz, 1H, H-5), 6.15 (s, 1H, H-3), 5.61 (d, *J* = 6.48 Hz, 1H, H-a), 3.51 (q, *J* = 6.48 Hz, 4H, H-7 & H-7'), 2.43 (s, 3H, H-g), 1.29 (t, *J* = 7.13 Hz, 3H, CH_3), 1.26 (t, *J* = 6.26 Hz, 6H, H-8 & H-8'); Anal. Calcd for $C_{17}H_{23}N_3O_3S$: C, 58.43; H, 6.63; N, 12.02, Found: C, 58.35; H, 6.60; N, 12.00.

2.2.2.6.Methyl-4-(4-(diethylamino)-2-hydroxyphenyl)-2-imino-6-methyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4f): Solid; mp: 132-135 ºC; IR (cm^{-1}): ν_{max} 3592 (OH), 3487-3390 (NH), 1627 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.56 (s, 1H, NH),10.33 (brs, 1H, H-d), 10.01 (brs, 1H, H-b), 9.47 (brs, 1H, -OH), 6.94 (d, *J* = 7.83 Hz, 1H, H-6), 6.48 (d, *J* = 5.41 Hz, 1H, H-5), 6.45 (s, 1H, H-3), 5.68 (d, *J* = 6.58 Hz, 1H, H-a), 3.58 (q, *J* = 6.64 Hz, 4H, H-7 & H-7'), 3.32 (s, 3H,-CH_3), 2.44 (s, 3H, H-g), 1.25 (t, *J* = 6.84 Hz, 6H, H-8 & H-8'); MS *m/z* (%): 332.18 (10.09), 345.37 (30.24), 282.62 (38.90), 165.28 (100.00), 108.18 (61.88), 31.23 (24.72), 15.19 (19.67); Anal. Calcd for $C_{17}H_{24}N_4O_3$: C, 61.43; H, 7.28; N, 16.86; Found: C, 61.35; H, 7.23; N, 16.82.

2.2.2.7. Ethyl -6-methyl-2-oxo-4-(4-(pyrrolidin-1-yl)phenyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (4g): Solid, mp: 133-135 ºC; IR (cm^{-1}): ν_{max} 3487-3409 (NH), 1659 (C=O), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.44 (brs,1H, H-d), 10.09 (brs, 1H, H-b), 6.93 (d, *J* = 7.76 Hz, 1H, H-6), 6.73 (s, 1H, H-2), 6.64 (d, *J* = 5.81 Hz, 1H, H-5), 6.19 (s, 1H, H-3), 5.63 (d, *J* = 6.68 Hz, 1H, H-a), 4.39 (q, *J* = 6.91 Hz, 2H, -CH_2), 3.53 (t, *J* = 6.44 Hz, 4H, H-7 & H-10), 2.45 (s, 3H, H-g), 1.37 (t, *J* = 7.16 Hz, 3H,-CH_3), 1.82 (t, *J* = 6.41 Hz, 4H, H-8 & H-9); MS *m/z* (%): 329.17 (20.0), 347.18 (19.28), 267.45 (19.93), 169.19 (100.00), 108.29 (61.70), 45.11 (36.62), 29.16 (21.84), 15.10 (30.33); Anal. Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76; Found: C, 65.55; H, 6.97; N, 12.71.

2.2.2.8.Ethyl-4-(4-(diethylamino)-3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4h): Solid; mp: 137-139 ºC; IR (cm^{-1}): ν_{max} 3589-3411 (NH), 759 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.28 (brs,1H, H-d), 10.03 (brs, 1H, H-b), 6.93 (d, *J* = 7.89 Hz, 1H, H-6), 6.75 (s, 1H, H-2), 6.67 (d, *J* = 5.71 Hz, 1H, H-5), 6.18 (s, 1H, H-3), 5.60 (d, *J* = 6.48 Hz, 1H, H-a), 4.40 (q, *J* = 6.93 Hz, 2H, CH_2), 3.52 (t, *J* = 6.48 Hz, 4H, H-7 & H-10), 1.39 (t, *J* = 7.18 Hz, 3H,-CH_3), 2.38 (s, 3H, H-g), 1.78 (t, *J* = 6.44 Hz, 4H, H-8 & H-9); MS *m/z* (%): 345.15 (21.0), 316.15 (21.46), 287.15 (54.97), 147.16 (100.00) 31.11 (23.52), 15.23 (34.67); Anal. Calcd for $C_{18}H_{23}N_3O_2S$: C, 62.58; H, 6.71; N, 12.16; Found: C, 62.51; H, 6.68; N, 12.12.

2.2.2.9.Ethyl-4-(4-(diethylamino)-3-hydroxyphenyl)-2-imino--6-methyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4i): Solid, mp: 167-169 ºC; IR (cm^{-1}): ν_{max} 3491-3411 (NH), 1623 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.56 (s, 1H, NH),10.31 (brs,1H, H-d), 10.01 (brs, 1H, H-b), 6.98 (d, *J* = 7.38 Hz, 1H, H-6), 6.73 (s, 1H, H-2), 6.33 (d, *J* = 5.88 Hz, 1H, H-5), 6.15 (s, 1H, H-3), 5.65 (d, *J* = 6.65 Hz, 1H, H-a), 4.36 (q, *J* = 6.95 Hz, 2H, CH_2), 3.55 (q, *J* = 6.56 Hz, 4H, H-7 & H-10), 2.42 (s, 3H, H-g), 1.29 (t, *J* = 7.14 Hz, 3H,-CH_3), 1.85 (t, *J* = 6.54 Hz, 4H, H-8 & H-9); MS *m/z* (%): 328.19 (30.09), 296.19 (61.70), 187.28 (100.00), 45.15 (35.26), 29.43 (33.16), 15.13 (38.18); Anal. Calcd for $C_{18}H_{24}N_4O_2$: C, 65.83; H, 7.37; N, 17.06; Found: C, 65.71; H, 7.33; N, 17.03.

2.2.2.10.Methyl-6-methyl-2-oxo-4-(4-(pyrrolidin-1-yl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j): Solid, mp: 128-130 ºC; IR (cm^{-1}): ν_{max} 3501-3403 (NH), 1661 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.33 (brs,1H, H-d), 10.01 (brs, 1H, H-b), 6.83 (d, *J* = 7.29 Hz, 1H, H-6), 6.74 (s, 1H, H-2), 6.22 (d, *J* = 5.1 Hz, 1H, H-5), 6.12 (s, 1H, H-3), 5.65 (d, *J* = 6.81 Hz, 1H, H-a), 3.51 (t, *J* = 6.57 Hz, 4H, H-7 & H-10), 3.33 (s, 3H,-CH_3), 2.45 (s, 3H, H-g), 1.87 (t, *J* = 6.75 Hz, 4H, H-8 & H-9); Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32; Found: C, 64.68; H, 6.68; N, 13.30.

2.2.2.11.Methyl-6-methyl-2-thioxo-4-(4-(pyrrolidin-1-yl)phenyl)-1,2,3,4-tetrahydro pyrimidine -5-carboxylate (4k): Solid; mp: 170-172 ºC; IR (cm^{-1}): ν_{max} 3489-3382 (NH), 757 (C=S), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.38 (brs,1H, H-d), 9.34 (brs, 1H, H-b), 6.87 (d, *J* = 8.02 Hz, 1H, H-6), 6.67 (s, 1H, H-2), 6.34 (d, *J* = 5.94 Hz, 1H, H-5), 6.02 (s, 1H, H-3), 5.88 (d, *J* = 7.68 Hz, 1H, H-a), 3.63 (t, *J* = 6.43 Hz, 4H, H-7 & H-10), 3.34 (s, 3H,-CH_3), 2.43 (s, 3H, H-g), 1.86 (t, *J* = 6.19 Hz, 4H, H-8 & H-9); Anal. Calcd for $C_{17}H_{21}N_3O_2S$: C, 61.61; H, 6.39; N, 12.68; Found: C, 61.56; H, 6.34; N, 12.61.

2.2.2.12.Methyl-2-imino-6-methyl-4-(4-(pyrrolidin-1-yl)phenyl)-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4l): Solid; mp: 144-146 ºC; IR (cm^{-1}): ν_{max} 3487-3384 (NH), 1632 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.68 (s, 1H, NH),10.23 (brs,1H, H-d), 9.81 (brs, 1H, H-b), 6.83 (d, *J* = 7.46 Hz, 1H, H-6), 6.68 (s, 1H, H-2), 6.28 (d, *J* = 5.92 Hz, 1H, H-5), 6.02 (s, 1H, H-3), 5.28 (d, *J* = 6.32 Hz, 1H, H-a), 3.24 (t, *J* = 7.12 Hz, 4H, H-7 & H-10), 3.21 (s, 3H,-CH_3), 2.53 (s, 3H, H-g), 1.79 (t, *J* = 6.88 Hz, 4H, H-8 & H-9); Anal. Calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82; Found: C, 64.05; H, 7.00; N, 17.81.

2.2.2.13.Ethyl-6-methyl-2-oxo-4-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4m): Solid; mp: 154-156 ºC; IR (cm^{-1}): ν_{max} 3490-3329 (NH), 1653 (C=O), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (brs,1H, H-d), 9.84 (brs, 1H, H-b), 6.82 (d, *J* = 6.38 Hz, 1H, H-6), 6.61 (s, 1H, H-2), 6.26 (d, *J* = 5.88 Hz, 1H, H-5), 6.10 (s, 1H, H-3), 5.73 (d, *J* = 6.87 Hz, 1H, H-a), 4.28 (q, *J* = 6.65 Hz, 2H, -CH_2), 3.44 (q, *J* = 6.38 Hz, 4H, H-9 & H-10), 3.18 (t, *J* = 6.64 Hz, 1H, H-7), 2.42 (s, 3H, H-g), 1.29 (t, *J* = 7.14 Hz, 3H,-CH_3), 1.20 (d, *J* = 6.19 Hz, 4H, H-8 & H-11) ; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.5 (C-h), 156.4 (C-2), 151.5 (C-c), 150.4 (C-4), 148.8 (C-e), 129.9 (C-6), 113.3 (C-1), 107.5 (C-f), 106.6 (C-5), 99.5 (C-3), 62.5 (<u>C</u>H_2), 54.7 (C-9 & C-10), 49.2 (C-a), 45.6 (C-7), 25.5 (C-8 & C-11), 18.8 (C-g), 15.6 (<u>C</u>H_3); MS *m/z* (%): 344.17 (20.50), 242.18 (51.08), 148.27 (100.00), 45.18 (46.69), 29.25 (41.34), 15.13 (22.56); Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13; Found: C, 66.17; H, 7.00; N, 8.10.

2.2.2.14.Ethyl-6-methyl-2-thioxo-4-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4n): Solid; mp: 169-171 ºC; IR (cm^{-1}): ν_{max} 3501-3373 (NH), 754 (C=S), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.39 (brs,1H, H-d), 10.07 (brs, 1H, H-b), 6.87 (d, *J* = 7.84 Hz, 1H, H-6), 6.59 (s, 1H, H-2), 6.26 (d, *J* = 5.54 Hz, 1H, H-5), 6.09 (s, 1H, H-3), 5.61 (d, *J* = 7.15 Hz, 1H, H-a), 4.37 (q, *J* = 6.73 Hz, 2H, CH_2), 3.87 (q, *J* = 6.58 Hz, 4H, H-9 & H-10), 3.10 (t, *J* = 6.19 Hz, 1H, H-7), 2.48 (s, 3H, H-g), 1.24 (t, *J* = 7.15 Hz, 3H, CH_3), 1.22 (9, *J* = 6.19 Hz, 6H, H-8 & H-11); MS *m/z* (%): 360.15 (20.43), 268.15 (22.72), 162.64 (14.28), 106.16 (100.00) 31.10 (42.27), 15.13 (18.76); Anal. Calcd for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77; Found: C, 63.25; H, 6.69; N, 7.73.

2.2.1.15.Ethyl-imino-6-methyl-2-4-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4o): Solid; mp: 142-144 ºC; IR (cm^{-1}): ν_{max} 3489-3370 (NH), 1618 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.57 (s, 1H, NH),10.28 (brs,1H, H-d), 9.06 (brs, 1H, H-b), 6.96 (d, *J* = 7.28 Hz, 1H, H-6), 6.58 (s, 1H, H-2), 6.26 (d, *J* = 5.87 Hz, 1H, H-5), 6.11 (s, 1H, H-3), 5.68 (d, *J* = 6.46 Hz, 1H, H-a), 4.32 (q, *J* = 6.82 Hz, 2H, -CH_2), 3.52 (t, *J* = 6.42 Hz, 4H, H-9 & H-10), 3.11 (t, *J* = 6.19 Hz, 1H, H-7), 2.42 (s, 3H, H-g), 1.27 (t, *J* = 7.14 Hz, 3H,-CH_3), 1.24 (t, *J* = 6.19 Hz, 4H, H-8 & H-11); Anal. Calcd for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24; Found: C, 66.37; H, 7.29; N, 12.21.

2.2.2.16.Methyl-6-methyl-2-oxo-4-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4p): Solid; mp: 151-153 ºC; IR (cm^{-1}): ν_{max} 3489-3364 (NH), 1662 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.41 (brs,1H, H-d), 10.09 (brs, 1H, H-b), 6.98 (d, *J* = 7.82 Hz, 1H, H-6), 6.34 (d, *J* = 6.14 Hz, 1H, H-5), 6.10 (s, 1H, H-3), 6.02 (s, 1H, H-2), 5.66 (d, *J* = 7.43 Hz, 1H, H-a), 3.56 (q, *J* = 6.48 Hz, 4H, H-9 & H-10), 3.26 (t, *J* = 6.58 Hz, 1H, H-7), 2.86 (s, 3H, H-g), 3.28 (s, 3H,-CH_3), 1.24 (d, *J* = 6.19 Hz, 4H, H-8 & H-11); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 49.8 (C-a), 152.4 (C-c), 148.2 (C-e), 107.6 (C-f), 18.3 (C-g), 169.5 (C-h), 55.6 (<u>C</u>H_3), 113.2 (C-1), 156.1 (C-2), 99.4 (C-3), 150.4 (C-4), 106.3 (C-5), 129.4 (C-6), 45.2 (C-7), 54.4 (C-9 & C-10), 25.5 (C-8 & C-11); Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48; Found: C, 65.40; H, 6.68; N, 8.43.

2.2.2.17.Methyl-6-methyl-2-thioxo-4-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4q): Solid; mp: 164-166 ºC; IR (cm^{-1}): ν_{max} 3486-3406 (NH), 759 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.33 (brs, 1H, H-d), 9.02 (brs, 1H, H-b), 6.74 (d, *J* = 7.83 Hz, 1H, H-6), 6.27 (d, *J* = 5.34 Hz, 1H, H-5), 6.18 (s, 1H, H-3), 6.06 (s, 1H, H-2), 5.67 (d, *J* = 6.46 Hz, 1H, H-a), 3.57 (q, *J* = 6.62 Hz, 4H, H-9 & H-10), 3.09 (t, *J* = 6.56 Hz, 1H, H-7), 2.44 (s, 3H, H-g), 3.24 (s, 3H,-CH_3), 1.28 (d, *J* = 6.38 Hz, 4H, H-8 & H-11); Anal. Calcd for $C_{18}H_{22}N_2O_3S$: C, 65.44; H, 6.71; N, 8.48; Found: C, 65.32; H, 6.66; N, 8.44.

2.2.2.18.Methyl-2-imino-6-methyl-4-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4r): Solid; mp: 163-165 ºC; IR (cm^{-1}): ν_{max} 3502-3413 (NH), 1619 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.65 (s, 1H, NH), 10.31 (brs, 1H, H-d), 10.11 (brs, 1H, H-b), 6.98 (d, *J* = 7.78 Hz, 1H, H-6), 6.28 (d, *J* = 5.66 Hz, 1H, H-5), 6.10 (s, 1H, H-3), 6.05 (s, 1H, H-2), 5.64 (d, *J* = 6.68 Hz, 1H, H-a), 3.56 (q, *J* = 6.48 Hz, 4H, H-9 & H-10), 3.48 (s, 3H,-CH_3), 3.18 (t, *J* = 6.84 Hz, 1H, H-7), 2.44 (s, 3H, H-g), 1.28 (d, *J* = 6.64 Hz, 4H, H-8 & H-11); MS *m/z* (%): 329.17 (30.09), 310.58 (19.82), 231.58 (52.15), 130.69 (100.00), 31.23 (29.42), 15.17 (47.63%); Anal. Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76; Found: C, 65.53; H, 6.97; N, 12.70.

2.3. Antimicrobial activity

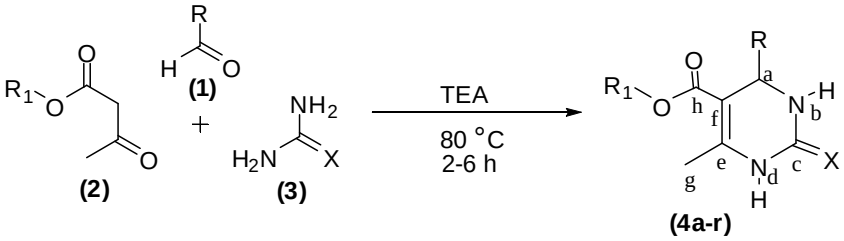
The compounds **4a-r** were screened by disc diffusion method[11, 12] for their antimicrobial activity against the bacteria, *Escherichia coli* and *Staphylococcus aureus* and fungi, *Aspergillus niger* and *Helminthosporium oryzae* by comparing with standard bactericide Penicillin and standard fungicide Griseofulvin at three different concentrations

(100, 50, 25 ppm). The tubes were incubated aerobically at 37ºC for 18-24h. The experiments were run in triplicates and the average results are included in Table 1.

RESULTS AND DISCUSSION

3.1. Chemistry

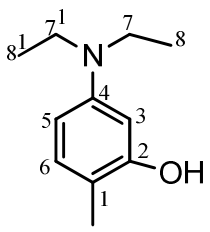
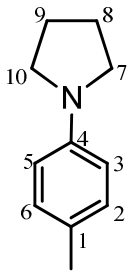
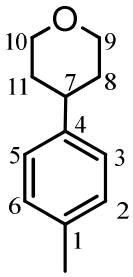
The preparation of 3, 4-dihydropyrimidin-2(*1H*)-ones/ thiones/ imines derivatives (**4a-r**) was accomplished in a single step. The synthetic route (**Scheme 1**) involves the condensation of various aryl aldehydes, ethyl/ methyl acetoacetate and Urea/ thiourea/ guanidine in the presence of triethylamine (TEA) at 80 ºC about 2-6 h to get the title compounds. The structural details of the synthesized compounds were given in **Figure 1**. All the synthesized compounds were characterized by spectral and elemental analysis.



Scheme 1: Synthesis of 4-aryl-3, 4-dihydropyrimidin-2(*1H*)-ones/ thiones/ imines (4a-r)

The absorption bands of the title compounds for their IR spectral characterization were observed at 3601-3591 cm^{-1} (O-H), 3589-3329 cm^{-1} (N-H), 1662-1653 cm^{-1} (C=O), 1632-1617 (C=N) and 759-754 cm^{-1} (C=S). In their ^1H NMR spectra, NH protons were resonated as singlet in the region of δ 10-68-9.34 ppm, and H-a proton as doublet in the region of δ 5.28-5.88 ppm. In their ^{13}C NMR spectra the C-c carbon resonated in the range of δ 152.4-151.2 ppm, the two alkenes carbons were observed in the range of δ 148.2-149.9 ppm, δ 107.3-108.8 ppm for C-e and C-f carbons respectively.

Figure 1: Structures of title compounds (4a-r)

Compound	R	R^1	X	Yield (%)	Melting Point (ºC)
4a		C_2H_5	O	80	143-145
4b		C_2H_5	S	81	168-170
4c		C_2H_5	NH	83	180-182
4d		CH_3	O	75	152-154
4e		CH_3	S	78	148-150
4f		CH_3	NH	76	132-135
4g		C_2H_5	O	79	133-135
4h		C_2H_5	S	86	137-139
4i		C_2H_5	NH	84	167-169
4j		CH_3	O	80	128-130
4k		CH_3	S	79	170-172
4l		CH_3	NH	73	144-146
4m		C_2H_5	O	71	154-156
4n		C_2H_5	S	77	169-171
4o		C_2H_5	NH	80	142-144
4p		CH_3	O	76	151-153
4q		CH_3	S	77	164-166
4r		CH_3	NH	82	163-165

3.2. Biology

All the titled compounds (**4a-r**) were screened for their antimicrobial activity, in this sequence first screened for the anti-bacterial activity against the growth of *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram –ve) at different concentrations (100, 50, 25 ppm) by disk diffusion method. All the compounds are good active against both the bacteria when compared to the reference compound Penicillin. Then next they are subjected for the antifungal activity evaluation against the growth of *Aspergillus Niger* and *Helminthosporium oryzae* at various concentrations (100, 50, 25 ppm) with Griseofulvin as the standard reference compound. The results of Zone of inhibition of title compounds (**4a-r**) were presented in **Table 1**. Majority of the title compounds showed good antifungal activity against both the fungi, especially **4g**, **4j**, **4m** and **4p** compounds showed good activity.

Table 1: Antimicrobial activity of the compounds 4a-r (µg/ mL)

Compound	Zone of inhibition (%)											
	Antibacterial activity						Antimicrobial activity					
	Escherichia coli			*Staphylococcus aureus*			*Aspergillus niger*			*Helminthosporium oryzae*		
	100	50	25	100	50	25	100	50	25	100	50	25
4a	22	11	5	22	11	7	15	10	7	14	9	5
4b	22	10	4	23	11	6	19	9	6	15	7	3
4c	22	10	5	21	10	6	19	10	5	14	6	6
4d	22	11	5	22	9	5	20	12	4	14	9	5
4e	22	11	6	21	12	6	18	11	6	13	7	4
4f	21	11	7	21	12	5	20	11	6	19	10	7
4g	23	12	7	23	10	6	21	10	6	20	11	6
4h	22	10	6	22	12	7	19	9	4	18	10	5
4i	21	10	5	22	10	6	18	11	7	13	8	4
4j	23	11	6	23	13	5	18	12	6	19	12	8
4k	22	10	5	21	10	6	17	10	5	14	6	6
4l	21	10	5	22	9	5	20	12	4	14	9	5
4m	23	12	6	23	12	6	19	11	6	13	7	4
4n	20	12	7	21	10	5	21	11	6	19	10	7
4o	21	10	5	20	10	6	20	10	5	19	11	6
4p	23	13	6	23	12	7	19	12	7	20	10	5
4q	21	10	5	22	11	6	20	11	7	13	8	4
4r	22	11	6	22	10	5	18	12	6	19	12	8
Penicillin	20	12	8	20	12	8						
Griseofulvin							20	10	5	20	10	5

CONCLUSION

We have reported the synthesis of new 4-aryl-3, 4-dihydropyrimidin-2(*1H*)-ones/ thiones/ imines with an environment-friendly methodology. The majority of the compounds (**4a-r**) exhibited significant activity against selective bacteria and fungi and the zone of inhibition of these title compounds was almost comparable to that of the standard drugs. Thus new group of compounds with comparable antimicrobial potency to the presently used commercial bactericides/ fungicides have been discovered.

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