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SYNTHESIS OF PYRIMIDINE CARBOXAMIDE DERIVATIVES CATALYZED BY URANYL NITRATE HEXA HYDRATE WITH THEIR ANTIBACTERIAL AND ANTIOXIDANT STUDIES

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ABSTRACT. An efficient and simple method was developed for the synthesis pyrimidine-5-carboxamides using $UO_2(NO_3)_2.6H_2O$ catalyst under conventional and microwave irradiation. The synthesis of dihydropyrimidine using uranyl nitrate had shown many advantages such as easy work up, shorter reaction times and higher yields using acetonitrile as a solvent. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. All the synthesized compounds screened for in vitro antioxidant and antibacterial activity and the results are reported.

KEY WORDS: Microwave, Uranyl nitrate, Antioxidant, Antibacterial

INTRODUCTION

Nitrogen based heterocycles provides broad range of biological activities; the lone pair present in the nitrogen atoms acts as donor facilitating the construction of various supramolecular blocks. Multi-component reactions (MCRs) are an important class of organic reactions, which is widely used to construct different target molecules in one pot reaction using three or more numbered starting materials. In 1893 an Italian chemist Pietro Biginelli has reported the synthesis of dihydropyrimidines by a simple one-pot cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea [1]. The literature reveals that Human kinesin Eg5, plays a crucial role in mitosis by establishing the bipolar spindle, which has been proved to be an interesting drug target for the development of cancer chemotherapeutics. In a similar way, monastrol, the first Biginelli compound, exhibited good anticancer property. Batzelladine A and B compounds of DHPMs derived [2] from natural marine sources, were the first low molecular weight natural products showing promising anti HIV activity and hence considered as potential molecules for treatment of AIDS.

The limited availability of the natural products renders them to be attractive targets for total synthesis [3]. The dihydropyrimidinone (DHPM) is the most important core structure in the synthesis of different medicinally and pharmacologically valuable agents such as antibacterial [4], antiviral [5], antitumor [6], antihypertensive agents [7], calcium channel blockers [8], neuropeptide Y (NPY) antagonists [9], α-1a-antagonists [10] and anti-inflammatory drugs [11]. In addition, the batzelladine alkaloids containing the DHPM ring structure inhibit the binding of HIV envelope protein gp-120 to human CD_4 cells and there are potential of new molecule for AIDS treatment [12-13]. Therefore, dihydropyrimidinones (DHPMs) synthesis always shows the attraction to organic chemists.

Biginelli reaction takes place by mixing different substituted aldehydes, urea or thiourea, and an active 1,3-dicarbonyl compound in combination with different catalytic systems such as AcOH [14], $ZrCl_4$ [15], $Cu(OTf)_2$ [16], SiO_2/H_2SO_4 [17], $La(OTf)_3$ [18], $CdCl_2$ [19], 1-n-butyl-3-methyl imidazolium tetrafluoroborate [20], $SiO_2/NaHSO_4$ [21], $Pb(NO_3)_2$ [22], NaCl [23], KSF

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clay [24], $FeCl_3$ [25], $BiCl_3$ [26], ion-exchange resin [27], LiBr [28], $AlCl_3.H_2O$ [29], *p*-TSA [30], $MgBr_2$ [31], $(NH_4)_2Ce(NO_3)_6$ [32], $Mn(OAc)_3$ [33], $InBr_3$ [34], microwave [35-38] or ultrasound irradiation [39] and solvent-free conditions [40], $Co(NO_3)_2.6H_2O$ [41], $ZnCl_2$/TBAB [42]. In the last two decades microwave mediated reactions have been of great interest in organic synthesis because of their shorter reaction times and high yields of products with good selectivity.

EXPERIMENTAL

General

All the reagents were purchased from Aldrich, SD Fine Chemicals and Qualigens and used without further purification. The ^{1}H NMR spectra were obtained on Bruker AV-500 MHz spectrometer with DMSO-d_6 as the solvent using tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were recorded at room temperature from 4000-400 cm^{-1} with KBr pellets at a resolution of 4 cm^{-1}, using Avatar 330 equipped with DTGS detector. The microwave irradiation experiments were carried out using conventional (unmodified) household microwave oven equipped with a turntable was used (LG, MG-395 WA, 760 W) and operating at 2450 MHz. Mass spectra were obtained using HRMS (JEOL 1600 HRMS). Melting points were determined by open capillaries and are uncorrected.

*General procedure for the preparation of compound 6-methyl-1,2,3,4-tetrahydro-N-aryl-2-thio/oxo-4-arylpyrimidine-5-carboxamide (**4a-o**)*

Conventional method. A mixture of aldehyde (1 mmol), acetoaetanilide (1 mmol), urea or thiourea (1.2 mmol), $UO_2(NO_3)_2.6H_2O$ (5 mol%) and 20 mL acetonitrile was refluxed as per duration time mentioned in Table 3. After completion of the reaction as indicated by TLC, the reaction mixture was poured into crushed ice, stirred for 15-20 min. and left overnight. The solid separated was filtered through a funnel, washed with ice-cold water and then recrystallized from hot methanol to afford pure compounds **4a-o**.

Microwave irradiation. A mixture of aldehyde (1 mmol), acetoaetanilide (1 mmol), urea or thiourea (1.2 mmol), $UO_2(NO_3)_2.6H_2O$ (5 mol%) and acetonitrile (5 mL) were taken in a small beaker and then the reaction mixture was subjected to microwave irradiation at an interval of 3 min at 160 W for about 15-18 min; varying time periods as shown in Table 3. The completion of the reaction was monitored by TLC. After the completion of the reaction, the mixture was poured into ice cold water stirred well and the solid separated was filtered, dried and then recrystallized from hot methanol to afford pure compounds **4a-o**.

*4-(3-Ethoxy-4-hydroxyphenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4c**)*. M.p. 253-256 ºC; IR (KBr) ν_{max}: 3542, 3259, 2977, 2931, 1701, 1660, 1609, 1591, 1581, 1518, 1491, 1478, 1436, 1411, 1371, 1336, 1281, 1225, 1212, 1155, 1121, 1093, 1062, 1041 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, ppm), δ_H = 9.10 (s, 1H, CONH), 8.86 (s, 2H, NH and OH), 7.53 (s, 1H, NH), 6.37–7.28 (m, 8H, ArH of phenyl ring), 5.23 (s, 1H, CH), 3.77-3.84 (m, 2H, OCH_2), 2.48 (s, 3H, CH_3), 1.18–1.32 (m, 3H, CH_3); ^{13}C NMR (125.757 MHz, DMSO-d_6, ppm), δ_C = 164.53, 163.35, 152.70, 152.57, 146.86, 146.76, 146.58, 146.49, 143.16, 142.04, 135.98, 132.26, 128.72, 127.35, 126.03, 125.54, 119.30, 118.02, 115.74, 115.59, 112.66, 102.58, 64.27, 64.17, 63.86, 53.17, 38.83, 15.26, 15.20; HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{21}N_3O_4$: 367.1532; found: 367.1531.

*4-(3-Ethoxy-4-hydroxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4d**)*. M.p. 242-245 ºC; IR (KBr) ν_{max}: 3349, 3192, 2975, 2931, 1672, 1625, 1595, 1571, 1512, 1467, 1435, 1400, 1283, 1234, 1217, 1189, 1149, 1120, 1108, 1084, 1039, 1012 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, ppm), δ_H = 10.29 (s, 1H, CONH), 9.52 (s, 1H, NH), 8.87–8.94

(split peak, 2H, NH and OH), 6.36-7.26 (m, 8H, ArH of phenyl ring), 5.25 (s, 1H, CH), 3.56-3.95 (m, 2H, OCH_2), 2.45 (s, 3H, CH_3), 1.18-1.35 (m, 3H, CH_3); HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{21}N_3O_3S$: 383.1304; found: 383.1302.

4-(2,4-Dichlorophenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide ***(4e)***. M.p. 206-209 ºC; IR (KBr) ν_{max}: 3397, 3265, 3168, 3084, 3006, 1669, 1626,1595, 1563, 1525, 1498, 1478, 1436, 1380, 1331, 1236, 1179, 1140, 1101, 1075, 1045 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, ppm), δ_H =10.11 (s, 1H, CONH), 9.86 (s, 1H, NH), 9.36 (s, 1H, NH), 7.56 (d, 1H, *J* = 2.5 Hz, *m*-ArH of phenyl ring), 7.50 (d, 3H, *J* = 7.5 Hz, *o,o′* and *m′*-ArH of phenyl ring), 7.38 (d, 1H, *J* = 8.5 Hz, *o′*-ArH of phenyl ring), 7.25 (t, 2H, *J* = 8.0 Hz, *m,m′*-ArH of phenyl ring), 7.02 (t, 1H, *J* = 7.25 Hz, *p*-ArH of phenyl ring), 5.75 (d, 1H, *J* = 2.0 Hz, CH), 2.02 (s, 3H, CH_3); ^{13}C NMR (100.612 MHz, DMSO-d_6, ppm), δ_C = 174.12, 164.36, 139.35, 138.77, 135.03, 133.08, 132.16, 130.83, 128.86, 128.02, 123.37, 119.47, 106.37, 52.42, 16.20; HRMS (EI): *m/z* [M^+] calcd. For $C_{18}H_{15}Cl_2N_3O_2$: 375.0541; found: 375.0541.

4-(2,4-Dichlorophenyl)-1,2,3,4-tetrahydro-6-methyl-N-phenyl-2-thioxopyrimidine-5-carboxamide ***(4f)***. M.p. 188-191 ºC; IR (KBr) ν_{max}: 3397, 3276, 3088, 2360, 2342, 1672, 1654, 1629, 1598, 1560, 1540, 1523, 1498, 1473, 1438, 1329, 1234,1202, 1180, 1143, 1101, 1076, 1046 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H =10.13 (s, 1H, CONH), 9.87 (s, 1H, NH), 9.37 (s, 1H, NH), 7.56 (d, 1H, *J* = 2.0 Hz, *m*-ArH of phenyl ring), 7.51 (d, 3H, *J* = 8.5 Hz, *o,o′* and *m′*-ArH of phenyl ring), 7.39 (d, 1H, *J* = 8.5 Hz, *o′*- ArH of phenyl ring), 7.26 (t, 2H, *J* = 8.0 Hz, *m,m′*-ArH of phenyl ring), 7.02 (t, 1H, *J* = 7.25 Hz, *p*-ArH of phenyl ring), 5.75 (d, 1H, *J* = 2.5 Hz, CH), 2.03 (s, 3H, CH_3); HRMS (EI): *m/z* [M^+] calcd. for $C_{18}H_{15}Cl_2N_3OS$: 391.0313; found: 391.0312.

4-(4-Ethoxy-3-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide ***(4g)***. M.p. 123-126 ºC; IR (KBr) ν_{max}: 3349, 3291, 3175, 3094, 2977, 2361, 1680, 1635, 1596, 1561, 1513, 1482, 1439, 1394, 1334, 1264, 1229, 1197, 1180, 1139, 1029 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 9.95 (s, 1H, CONH), 9.72 (s, 1H, NH), 9.38 (s, 1H, NH), 7.54 (d, 2H, *J* = 8.5 Hz, *o,o′*-ArH of phenyl ring), 7.26 (t, 2H, *J* = 7.25 Hz, *m,m′*-ArH of phenyl ring), 7.02 (t, 1H, *J* = 7.25 Hz, *p*-ArH of phenyl ring), 6.91 (d, 1H, *J* = 8.0 Hz, *o*-ArH of phenyl ring), 6.85 (s, 1H, *m'*-ArH of phenyl ring), 6.78 (d, 1H, *J* = 8.0 Hz, *o′*-ArH of phenyl ring), 5.36 (s, 1H, CH), 3.96 (q, 2H, *J* = 6.75 Hz, OCH_2), 3.67 (s, 3H, OCH_3), 2.07 (s, 3H, CH_3), 1.29 (t, 3H, *J* = 6.75 Hz, CH_3); HRMS (EI): *m/z* [M^+] calcd. for $C_{21}H_{23}N_3O_3S$: 397.1460; found: 397.1459.

6-Methyl-2-oxo-N-phenyl-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide ***(4h)***. M.p. 192-195 ºC; IR (KBr) ν_{max}: 3249, 2362, 1697, 1640, 1592, 1509, 1492, 1452, 1396, 1307, 1286, 1251, 1208, 1148, 1089, 1040, 1012 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 9.57 (s, 1H, CONH), 8.85 (s, IH, NH), 7.80 (s, 1H, NH), 7.58 (d, 2H, *J* = 8.0 Hz, *o,o′*-ArH of phenyl ring), 6.93–7.38 (m, 6H, ArH of phenyl and thiophene ring), 5.59 (d, 1H, *J* = 3.0 Hz, CH), 2.06 (s, 3H, CH_3); HRMS (EI): *m/z* [M^+] calcd. For $C_{16}H_{15}N_3O_2S$: 313.0885; found: 313.0884.

6-Methyl-N-phenyl-4-(thiophen-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide ***(4i)***. M.p. 201-204 ºC; IR (KBr) ν_{max}: 3368, 3284, 1679,1635, 1566, 1548, 1523, 1499, 1477, 1439, 1360, 1328, 1232, 188, 1117, 1076, 1037 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, ppm), δ_H =10.14 (s, 1H, CONH), 9.73 (s, 1H, NH), 9.62 (s, 1H, NH), 6.95-7.68 (m, 8H, ArH of phenyl and thiophene ring), 5.67 (d, 1H, *J* = 3.0 Hz, CH), 2.10 (s, 3H, CH_3); ^{13}C NMR (100.612 MHz, DMSO-d_6, ppm), δ_C = 174.19, 164.53, 146.91, 138.94, 136.61, 128.54, 126.78, 125.67, 124.29, 123.34, 119.74, 107.07, 50.36, 16.55; HRMS (EI): *m/z* [M^+] calcd. for $C_{16}H_{15}N_3OS_2$: 329.0657; found: 329.0656.

4-(4-Ethoxyphenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide ***(4j)***. M.p. 235-238 ºC; IR (KBr) ν_{max}: 3249, 3114, 2981, 2927, 2597, 1736, 1666, 1628, 1611, 1597, 1516, 1440, 1392, 1358, 1328, 1267, 1247, 1176, 1170, 1074, 1048, 1008 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ppm), δ_H = 9.52 (s, 1H, CONH), 8.70 (s, 1H, NH proton), 6.84-7.55 (m, 10H, NH and ArH of phenyl ring), 5.36 (s, 1H, CH), 3.98 (t, *J* = 6.90 Hz, 2H, OCH_2), 2.04 (s, 3H, CH_3), 1.28 (t, 3H, *J* = 6.90 Hz, CH_3); ^{13}C NMR (100.612 MHz, DMSO-d_6, ppm), δ_C = 172.04, 165.31, 157.75, 152.49, 139.21, 138.15, 136.27, 128.46, 127.47, 123.00, 119.50, 114.19, 105.58, 62.91, 54.46, 16.98, 14.60; HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{21}N_3O_3$: 351.1583; found: 351.1582.

4-(4-Hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide ***(4k)***. M.p. 230-233 ºC; IR (KBr) ν_{max}: 3411, 3285, 2363, 2341, 1683, 1653, 1628, 1597, 1539, 1521, 1487, 1442, 1386, 1330, 1262, 1241, 1164, 1124, 1074, 1034 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ppm), δ_H = 9.53 (s, 1H, CONH), 8.93 (s, 1H, OH), 8.67 (s, 1H, NH), 6.71–7.56 (m, 9H, NH and ArH of phenyl ring), 5.34 (s, 1H, CH), 3.67 (s, 3H, OCH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR (100.612 MHz, DMSO-d_6, ppm), δ_C = 165.46, 152.51, 147.32, 145.80, 139.19, 137.88, 135.18, 128.47, 123.04, 119.52, 118.47, 115.21, 110.71, 105.56, 55.46, 54.75, 16.95; HRMS (EI): *m/z* [M^+] calcd. for $C_{19}H_{19}N_3O_4$: 353.1376; found: 353.1374.

N-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide ***(4l)***. M.p. 205-208 ºC; IR (KBr) ν_{max}: 3397, 3195, 1673, 1630,1596, 1565, 1530, 1469, 1439, 1383, 1235, 1202, 1102, 1046 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 9.84 (s, 1H, CONH), 8.88 (s, 1H, NH), 7.58 (s, 1H, NH), 7.52-7.55 (m, 3H, *o,o′* and *m*-ArH of phenyl ring), 7.45 (d, 2H, *J* = 2.0 Hz, *m,m′*-ArH of phenyl ring), 7.28-7.30 (split peak, 2H, *o′* and *m′*-ArH of phenyl ring), 5.75 (d, 1H, *J* = 2.0 Hz, CH), 2.02 (s, 3H, CH_3); HRMS (EI): *m/z* [M+] calcd. for $C_{18}H_{14}Cl_3N_3O_2$: 409.0152; found: 409.0151.

N-(4-Chlorophenyl)-4-(4-ethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide ***(4m)***. M.p. 248-251 ºC; IR (KBr) ν_{max}: 3293, 2981, 2926, 1702, 1659, 1618, 1585, 1513, 1492, 1477, 1412, 1396, 1376, 1341, 1303, 1272, 1241, 1177, 1137, 1115, 1093, 1049 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 9.16 (d, 1H, CONH), 7.60 (t, 1H, *J* = 2.25 Hz, NH), 6.63-7.31 (m, ArH and NH protons), 5.13-5.29 (split peak, 1H, CH), 3.95-4.03 (m, 2H, OCH_2), 2.46-2.51 (m, 3H, CH_3), 1.29-1.35 (m, 3H, CH_3); HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{20}ClN_3O_3$: 385.1193; found: 385.1192.

N-(4-Chlorophenyl)-4-(4-ethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide ***(4n)***. M.p. 228-230 ºC; IR (KBr) ν_{max}: 3199, 2978, 2925, 1673, 1616, 1560, 1512, 1492, 1464, 1411, 1395, 1338, 1304, 1252, 1197, 1182, 1162, 1111, 1092, 1047, 1014 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 10.35 (s, 1H, CONH), 9.51 (s, 1H, NH), 7.31-7.33 (split peak, 1H, NH), 7.12-7.14 (split peak, 2H, *o,o′*-ArH of phenyl ring), 7.00 (d, 2H, *J* = 3.5 Hz, *m,m′*-ArH of phenyl ring), 6.81-6.87 (m, 2H, ArH of phenyl ring), 6.64 (d, 2H, *J* = 9.0 Hz, ArH of phenyl ring), 5.62 (s, 1H, CH), 3.94–4.04 (m, 2H, OCH_2), 2.16 (s, 3H, CH_3), 1.30-1.35 (m, 3H, CH_3); HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{20}ClN_3O_2S$: 401.0965; found: 401.0964.

N-(4-Chlorophenyl)-6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide ***(4o)***. M.p. 239-224 ºC; IR (KBr) ν_{max}: 3245, 3103, 1664, 1594, 1529, 1491, 1427, 1398, 1307, 1240, 1187, 1091, 1042, 1012 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 10.12 (s, 1H, CONH), 8.95 (s, 1H, NH), 7.95 (s, 1H, NH), 7.63–7.65 (split peak, 2H, *o,o′*-ArH of phenyl ring), 7.51-7.59 (split peak, 2H, *m,m′*-ArH of phenyl ring), 6.95-7.42 (m, 3H, ArH of thiophene ring), 5.73 (d, 1H, J = 3.0 Hz, CH), 2.08 (s, 3H, CH_3); HRMS (EI): m/z [M^+] calcd. for $C_{16}H_{14}ClN_3O_2S$: 347.0495; found: 347.0494.

Screening of antioxidant activity

The radical-scavenging activity of synthesized compound was evaluated and compared to that of butylated hydroxyl toluene (BHT) and ascorbic acid using the DPPH radical scavenging assay. This assay is based on the measurements of the scavenging ability of compounds towards the stable radical DPPH. The disappearance of absorption of this commercially available radical is measured spectrophotometrically at 517 nm in a dimethyl sulphoxide (DMSO) solution using a UV/Vis-spectrophotometer under thermo-static conditions at 25 ºC. DPPH has an odd electron and hence has a strong absorption band at 517 nm. When this electron becomes paired off, the absorption decreases stoichiometrically with respect to the number of electrons or hydrogen atoms taken up. Such a change in the absorbance by this reaction has been extensively adopted to test the capacity of several molecules to act as free radical scavengers. Hence, faster is the decrease of absorbance; more pronounced is the antioxidant activity of the compound.

3.0 mL of a freshly prepared DPPH solution of 6.02 x 10^{-5} M in DMSO was placed in a test tube and 100 µL of a DMSO solution of each test compound added. After that the solution was kept at room temperature for 30 min in dark and the absorbance was measured at 517 nm. The control contained all the reaction reagents except the synthetic compound or positive control substance. The experiment was carried out in triplicate and average values are reported. The DPPH scavenging activity was expressed as the inhibition of free radical DPPH in percent (I %) as described by Tepe *et al.* [43].

$$\text{Inhibition (\%)} = [(\text{control OD} - \text{sample OD})/\text{control OD}] \times 100.$$

Screening of antibacterial activity

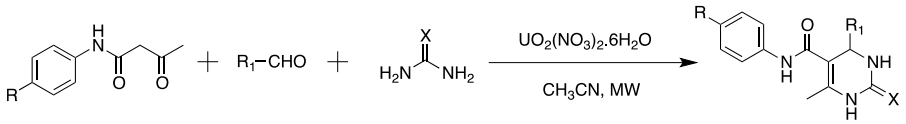
The *in vitro* antibacterial studies were carried out against three "Gram +ve" bacterial strains, *Staphylococcus aureus* (MTCC 3381), *Pseudomonas aeruginosa* (MTCC 2295) and *Bacillus cereus* (MTCC 8372) and two "Gram -ve" bacterial strains, *Escherichia coli* (MTCC 1302), *Klebsiella pneumonia* (MTCC 3384) by agar well diffusion method using Muller Hinton agar as the medium [44]. A number of antimicrobial discs were placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. 20 mL of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing them in an incubator at 37 ^{o}C for an hour. Using a punch, wells were made on these seeded agar plates and different concentrations of the test compounds in dimethylsulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using DMSO as solvent. All the plates were incubated at 37 ^{o}C for 24 h. The degree of effectiveness was measured by determining the diameters of the zone of inhibition produced by the compounds. Activity of each compound was compared with standard drug ampicillin available in the market. Minimum inhibitory concentration (MIC) was calculated as the lowest concentration of the sample at which there is no visible growth of the bacteria.

RESULTS AND DISCUSSION

In the present work a simple, efficient and practical approach for the synthesis of 4-aryl pyrimidine-5-carboxamide by reacting actoacetanilide, urea or thiourea with substituted benzaldehyde using $UO_2(NO_3)_2.6H_2O$ under conventional and microwave irradiation methods are reported (Scheme 1). $UO_2(NO_3)_2.6H_2O$ is a cost effective catalyst for the synthesis of 5-carboxamide-DHPM compounds compared to the other Lewis acid catalysts reported in the literature.

The optimized reaction condition was developed using condensation of benzaldehyde, urea and acetoacetanilide in the presence of catalytic amounts of $UO_2(NO_3)_2.6H_2O$ under conventional and microwave irradiations using different solvent system such as chloroform,

dichloromethane, ethanol, methanol, acetonitrile and different catalytic mole percent was also examined and the results are reported (Table 1 and 2).



R = H, Cl, X = O, S; R_1 = 2,4-dichlorophenyl, 4-ethoxyphenyl, 3-ethoxy-4-hydroxylphenyl, 3-methoxy-4-hydroxylphenyl, 2-thiophene

Scheme 1. Facile one pot synthesis of 6-methyl-1,2,3,4-tetrahydro-*N*-aryl-2-oxo-4-aryl pyrimidine-5-carboxamide derivatives (**4a-o**) catalyzed by $UO_2(NO_3)_2.6H_2O$.

Table 1. Effect of solvent[a].

S. No.	Solvents	Catalyst (mol %)	Time (min)	Yield (%)
1	Chloroform	5	25	33
2	Dichloromethane	5	25	29
3	Ethanol	5	16	75
4	Methanol	5	16	73
5	Acetonitrile	5	15	91

[a]Aldehyde (1 mmol), acetoaetanilide (1 mmol), urea or thiourea (1.2 mmol), $UO_2(NO_3)_2.6H_2O$ (5 mol%), 800 W.

Table 1 indicates that polar solvents such as methanol, ethanol and acetonitrile, gave better yields when compared to non polar ones, which indicate that acetonitrile is the best solvent for this conversion.

Table 2. Effect of catalysts loading[a].

S. No	Catalyst	Catalyst (mol %)	Time (min)	Yield (%)
1	$UO_2(NO_3)_2.6H_2O$	5	15	91
2	$UO_2(NO_3)_2.6H_2O$	10	15	91
3	$UO_2(NO_3)_2.6H_2O$	15	15	91
4	Conc. HCl	1 mL	16 h	63

The results are shown that the reaction proceed more efficiently under microwave irradiation when compared to conventional heating. Furthermore, effect of catalyst loading was studied. The optimum catalyst mole percent was found to be 5 mol %, when we increasing the catalyst mole percent (**1** and **2**, Table 2) did not show any improvement in the yield percent. After optimization of the reaction conditions, this method was used for synthesis of DHPM using different substituted aldehydes, urea or thiourea and substituted acetoacetanilide under conventional heating and microwave irradiation conditions to synthesis of new DHPM derivatives by using $UO_2(NO_3)_2.6H_2O$ as a catalyst for this reaction (Table 3).

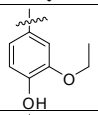
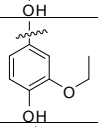
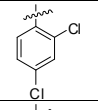
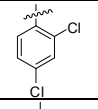
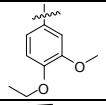
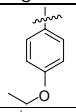
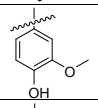
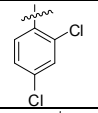
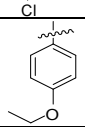
The catalyst which is highly soluble in water could be easily removed by washing with excess amount of cold water through suction filtration. All the synthesized compounds characterized through IR, ^{1}H NMR and HRMS mass spectra.

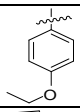
Antioxidant activity

Antioxidant activities of all the newly synthesized compounds **4a-o** was carried out using DPPH free radical scavenging assay method. The antioxidant studies revealed that compound **4c**, **4d**, **4f** and **4g** show reasonable free radical scavenging activity (70.88, 71.45, 76.34, and 72.60%, respectively) compared to that of BHT (butylated hydroxyl toluene) and ascorbic acid (100%), while that compound **4e**, **4k** and **4o** shows good activity, while that compounds **4a**, **4b**, **4h**, **4i**,

4j, **4l**, and **4m** do not show antioxidant activity at 100 µg/mL concentration at 1 hour incubation time. Compound **4c** and **4d** having phenolic OH in their substitution this have contributed to better antioxidant activity.

Table 3. Experimental results and physical data of 6-methyl-1,2,3,4-tetrahydro-N-aryl-2-oxo/thio-4-arylpyrimidine-5-carboxamide derivatives **4a-o**.

Compound	R	R_1	X	Reaction time (min)		Yield (%)[a]		m.p. (°C)
				MW	Conv.	MW	Conv.	
4a	H		O	15	450	91	82	225-228 [41]
4b	H		S	16	450	90	83	214-217 [41]
4c	H		O	17	480	86	80	253-256
4d	H		S	18	480	83	78	242-245
4e	H		O	18	480	85	79	206-209
4f	H		S	19	480	83	75	188-191
4g	H		S	19	480	83	76	123-126
4h	H		O	18	420	86	77	192-195
4i	H		S	18	420	82	75	201-204
4j	H		O	19	450	87	80	235-238
4k	H		O	19	420	89	85	230-233
4l	4-Cl		O	17	480	88	79	205-208
4m	4-Cl		O	17	480	89	78	248-251

4n	4-Cl		S	18	480	85	75	228-230
4o	4-Cl		O	18	420	88	77	239-242

[a]Aldehyde (1 mmol), acetoaetanilide (1 mmol), urea or thiourea (1.2 mmol), 5 mL acetonitrile.

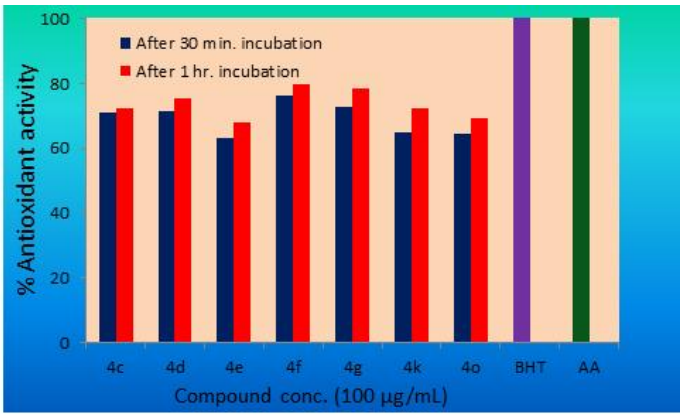


Figure 1. Comparsion of antioxidant activity of compounds **4a-o**, BHT and ascorbic acid using DPPH radical scavenging method after 30 min and 1 h incubation.

Free radical scavenging capacities of the synthesized compounds **4a-o**, BHT and ascorbic acid at 100 µg/mL concentration after half an hour and 1 hour incubation time in dark at room temperature are shown in Figure 1. The radical scavenging activity (RSA) for methanolic solutions of synthesized compounds **4a-o** are presented in (Table 4) and compared with those of standards BHT and ascorbic acid.

Table 4. Antioxidant activity of compounds **4a-o** using DPPH radical scavenging method.

After 30 min incubation*			After 1 h incubation		
Compound	Absorbance	% Antioxidant activity	Compound	Absorbance	% Antioxidant activity
4c	2.03	70.88	**4c**	1.92	72.47
4d	1.99	71.45	**4d**	1.74	75.13
4e	2.58	63.02	**4e**	2.25	67.81
4f	1.65	76.34	**4f**	1.41	79.77
4g	1.91	72.60	**4g**	1.50	78.53
4k	2.45	64.86	**4k**	1.92	72.48
4o	2.50	64.23	**4o**	2.14	69.33
Control**	7.00				

*BHT and ascorbic acid was used as a standard antioxidant. ** DPPH in DMSO.

Antibacterial activity

Antibacterial activity screening of all the synthesized compounds **4a-o** against different "Gram +ve" bacterial strains *S. aureus* (MTCC 3381), *P. aeruginosa* (MTCC 2295) and *B. cereus* (MTCC 8372) and two "Gram -ve" bacterial strains *E. coli* (MTCC 1302), *K. pneumonia* (MTCC 3384) organisms by zone inhibition method.

The compounds **4c**, **4g**, **4h** and **4k** shows highest activity against *S. aureus*, *P. aeruginosa*,

E. coli and *K. pneumonia* and moderate activity against *B. cereus* while compounds **4d** and **4j** showed good activity against *B. cereus* and moderate activity against other bacterial strains. The compounds **4d** and **4o** show moderate activity against *P. aeruginosa* and *K. pneumonia* and least activity against other organisms. Compounds **4a**, **4b**, **4e**, **4f**, **4i**, **4j**, **4l** and **4n** show least activity against all the micro organisms screened. The data on the antibacterial activity of these compounds is given in Table 5.

Table 5. Antibacterial activities of the synthesized compounds **4a-o**.

Compound	Zone of bacterial inhibition in[a] (mm)									
	E. coli		*K. pneumonia*		*B. cereus*		*P. aeruginosa*		*S. aureus*	
	25 µg/mL	50 µg/mL	25 µg/mL	50 µg/mL	25 µg/mL	50 µg/mL	25 µg/mL	50 µg/mL	25 µg/mL	50 µg/mL
4a	9	10	8	10	10	11	10	12	9	11
4b	10	12	9	11	8	10	9	11	10	11
4c	13	15	10	13	10	12	11	15	12	14
4d	12	14	11	13	12	14	11	14	11	14
4e	11	13	9	11	10	12	12	13	10	13
4f	9	11	9	10	9	12	10	11	10	11
4g	13	16	11	14	10	13	13	15	12	15
4h	12	13	10	14	8	11	10	13	9	13
4i	10	12	9	11	10	12	9	12	11	14
4j	10	12	9	11	11	13	10	11	8	10
4k	11	15	12	14	11	13	13	15	11	14
4l	8	10	7	9	8	9	10	12	9	11
4m	10	13	9	12	11	12	12	14	9	11
4n	9	11	10	11	10	13	11	13	10	12
4o	11	13	12	13	10	12	12	14	9	11
Ampicilin[b]	19		17		16		18		16	

[a]Zone of inhibition in mm. [b]Standard antibacterial drug (25 µg/mL).

CONCLUSION

A simple and efficient procedure for the synthesis of 6-methyl-1,2,3,4-tetrahydro-N-aryl-2-oxo/thio-4-arylpyrimidine-5-carboxamide derivatives by one-pot three-component condensation of different substituted aldehydes, urea or thiourea and substituted acetoacetanilides under conventional heating and microwave irradiation conditions using $UO_2(NO_3)_2.6H_2O$ as catalyst has been presented. The main advantages of this process such as mild reaction conditions, shorter reaction times, cost effective catalyst, easy work-up and high yields. The synthesized compounds **4a-o** were screened for their *in vitro* antioxidant activity using DPPH free radical scavenging method. The compound **4e**, **4k** and **4o** shows good antioxidant activity when compared to other synthesized compounds. Antibacterial activity of the synthesized compounds also carried out and it was observed that compounds **4c**, **4g**, **4h** and **4k** showed highest activity against *S. aureus*, *P. aeruginosa*, *E. coli* and *K. pneumonia* remaining compound showed moderate activity in comparison with standard drug.

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REFERENCES

1. Biginelli, P. *Gazz. Chim. Ital.* **1893**, 23, 360.
2. Patil, A.D.; Kumar, N.V.; Truneh, D.; Faulkner, J.; Carte, B.; Breen, A.L.; Hertzberg, R.P.;

Johnson, R.K.; Westley, J.W.; Potts, B.V. *J. Org. Chem.* **1995**, 60, 1182.
3. Kim, J.; Park, C.; So, W.; Jo, M.; Seo, M.; Kim, Y.; Sohn, J.H.; Park, Y.; Han, S.J.; Kim, T.H. *Bioorg. Med. Chem. Lett.* **2012**, 22, 2522.
4. Kappe, C.O. *Acc. Chem. Res*. **2000**, 33, 879.
5. Lusch, M.J.; Tallarico, J.A. *Org. Lett.* **2004**, 6, 3237.
6. Mohammad, M.; Mymoona, A.; Asif, H.; Akranth, M.; Rashiduddin, H.; Mohammad, S. *Acta. Pol. Pharm. Drug. Res*. **2012**, 69, 1077.
7. Adlapalli, R.K.; Chourasia, O.P.; Vemuri, K.; Sritharan, M.; Perali R.S. *Bioorg. Med. Chem. Lett*. **2012**, 22, 2708.
8. Zhu, L.; Cheng, P.; Sheng, C.; Zhuang, C.; Guo, W.; Liu, W.; Zhang, Y.; Dong, G.; Wang, Z.; Miao, Z.; Zhang, W. *Arch. Pharm*. **2011**, 344, 726.
9. Bhushan, N.; Vasant, S.; Sanjeev, R. *Curr. Chem. Lett*. **2012**, 1, 59.
10. Patil, A.D.; Freyer, A.J.; Taylor, P.B.; Carté, B.; Zuber, G.; Johnson, R.K.; Faulkner, D.J. *J. Org. Chem.* **1997**, 62, 1814.
11. İnci, S.Z.; Selma, S.; Semra, C.; Kevser, E. *Bioorg. Med. Chem*. **2006**, 14, 8582.
12. Snider, B.B.; Chen, J.; Patil, A.D.; Freyer, A. *Tetrahedron Lett.* **1996**, 37, 6977.
13. Rama Rao, A.V.; Gujar, M.; Vasudevan, J. *J. Chem. Soc. Chem. Commun*. **1995**, 1369.
14. Mamedov, V.A.; Mustakimova, L.V.; Gubaidullin, A.T.; Vdovina, S.V.; Litvinov I.V.; Reznik V.S. *Chem. Heterocycl. Comp*. **2006**, 42, 1229.
15. Reddy, C.V.; Mahesh, M.; Babu, T.R.; Reddy, V.N. *Tetrahedron Lett.* **2002**, 43, 2657.
16. Prabhakar, A.S.; Dewkar, G.K.; Sudalai, A. *Tetrahedron Lett*. **2003**, 44, 3305.
17. Wu, L.; Yan, F.; Yang, C.; *Bull. Chem. Soc. Ethiop*. **2010**, 24, 417.
18. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, 65, 3864.
19. Kappe, C.O.; Kumar, D.; Varma, R.S. *Synthesis* **1999**, 1999, 1799.
20. Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, 42, 5917.
21. Chari, A.M.; Syamasundar, K. *J. Mol. Catal. A* **2004**, 221, 137.
22. Boumoud, C.; Boumoud, B.; Rhouati, S.; Belfaitah, A.; Debache, A.; P. Mosset, P. *E-J. Chem.* **2008**, 5, 688.
23. Kolosov, M.A.; Orlov, V.D.; Beloborodov, D.A.; Dotsenko, V.V. *Mol. Diver.* **2009**, 13, 5.
24. Bigi, F.; Carloni, S.; Frulanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett*. **1999**, 40, 3465.
25. Lu, J.; Bai, Y. *Synthesis* **2002**, 2002, 466.
26. Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T.N.B. *Synlett* **2001**, 2001, 863.
27. Bussolari, J.C.; McDonnell, P.A. *J. Org. Chem.* **2000**, 65, 6777.
28. Maiti, G.; Kundu, P.; Guin, C. *Tetrahedron Lett.* **2003**, 44, 2757.
29. Kumar, D.; Suresh, D.; Sandhu, J.S. *Ind. J. Chem.* **2010**, 45B, 360.
30. Phucho, I.T.; Tumtin, S.; Nongpiur, A.; Nongrum, R.; Nongkhlaw, R.L. *J. Chem. Pharm. Res.* **2010**, 2, 214.
31. Salehi, H.; Guo, Q.X. *Synn. Comm.* **2004**, 34, 171.
32. Yadav, J.S.; Reddy, K.B.; Raj, K.S.; Prasad, A.R. *J. Chem. Soc. Perkin Trans. I* **2001**, 2001, 1939.
33. Kumar, K.A.; Kasthuraiah, M.; Reddy, C.S.; Reddy, C.D. *Tetrahedron Lett.* **2001**, 42, 7873.
34. Fu, N.Y.; Yuan, Y.F.; Cao, Z.; Wang, J.T.; Peppe, C. *Tetrahedron* **2002**, 58, 4801.
35. Yadav, J.S.; Reddy, B.V.S.; Reddy, E.J.; Ramalingam, T. *J. Chem. Res.* **2000**, 2000, 354.
36. Stefani, H.A.; Gatti, P.M. *Syn. Comm*. **2000**, 30, 2165.
37. Choudhary, V.R.; Tillu, V.H.; Nasrkhede, V.S.; Borate, H.B.; Wakharkar, R.D. *Catal. Comm*. **2003**, 4, 449.
38. Mirza-Aghayan, M.; Bolourtchian, M.; Hosseini M. *Syn. Comm.* **2004**, 34, 3335.
39. Li, J.T.; Han, J.F.; Yang, J.H.; Li, T.S. *Ultrason. Sonochem.* **2003**, 10, 119.
40. Reddy, K.R.; Reddy, C.V.; Mahesh, M.; Raju, P.V.K. *Tetrahedron Lett.* **2003**, 44, 8173.
41. Nasr-Esfahani, M.; Montazerozohori, M.; Aghel-Mirrezaee, M.; Kashi, H. *J. Chil. Chem. Soc.* **2014**, 59, 2311.
42. Surendranatha Reddy, O.; Venkata Suryanarayana, Ch.; Sharmila, N.; Ramana, G.V.; Anuradha V.; Hari Babu, B. *Lett. Drug. Des. Discov*. **2016**, 10, 699.
43. Tepe, B.; Sokmen, M.; Akpulat, H.A.; Sokmen, A. *Food Chem*. **2006**, 95, 200.
44. Venkatesan, K.; Satyanarayana, V.S.V.; Sivakumar, A. *Bull. Chem. Soc. Ethiop*. **2012**, 26, 257.