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ARTICLE

PTSA-Catalyzed One Pot Domino Synthesis of Dihydropyrido[2,3-*d*]pyrimidine Derivatives and their Antimicrobial Activity

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ABSTRACT

A novel series of dihydropyrido[2,3-*d*]pyrimidine derivatives were synthesized by multicomponent domino cyclization *via* the one-pot three component reaction of 6-amino uracil, substituted aryl aldehydes and *N*-methyl-1-(methylthio)-2-nitroethenamine in the presence of PTSA 10 mol% as a catalyst. The structures of these synthesized compounds were characterized by spectral analysis. Further the synthesized compounds screened for *in vitro* antimicrobial activity. Among all the compounds, compound **4b** containing flouro substitution exhibited good inhibition against the tested species.

KEYWORDS

Pyrido[2,3-*d*]pyrimidine, PTSA, One-pot synthesis.

INTRODUCTION

Organic compounds having heterocycles wide spectrum in natural product, vitamins, hormones, dyes, agrochemical, antibiotics, pharmaceutical chemistry [1,2]. Nitrogen containing heterocycles especially pyrimidine molecules has been given more attention because of their main skeleton in natural product, alkaloids and nucleic bases in biologically active products and depict considerable therapeutic potential.

Pyrido[2,3-*b*]pyrimidines have pyrimidine based hydride scaffolds great importance due to their broad biological and medicinal applications. For the pharmaceutical and industries pyrido[2,3-*b*]pyrimidines derivatives shown potential biological activities such as antibacterial [3], antifungal [4], antihypertensive [5], antitumor [6], analgesic [7], anticonvulsant [8], antihistaminic [9], antileishmanial [10]. They are also useful in tyrosine kinase inhibitors [11,12], Eukaryotic elongation factor-2 kinase [13], Angiotensin II antagonists [14], calcium channel antagonist [15], *etc*.

Uracil is one of the most active pharmacophores in the medicinal chemistry as naturally occurring pyrimidine derivatives. In ribonucleic acid (RNA), uracil is a one of the four nucleobase [16]. Uracil derivatives have been enhance more physiological effect and organic compounds give different types of activity because of strong binding to various biological targets. Uracil derivatives have been act as tyrosine kinase inhibitor [17,18], adenosine kinase inhibitors [19] and calcium channel antagonist.

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Nowadays, the development of multicomponent reactions (MCRs) has become a most prominent strategy because reduced of synthesis step, higher yield, less toxic chemical use, reduced waste, shorter reaction time and simple isolation process [20, 21]. Thus, MCRs have very significant reactions and used for generation of key structural scaffolds for the synthesis of pharmacological active heterocyclic compounds and industrial use [22-25].

Various type of ketene acetals are reported in the literature, among them *N,S*-acetals having widely used in synthetic chemistry as well as biological active compounds [26,27]. Different types of ketene *N,S*-acetals derivatives having different substituent and useful for the synthesis of the various lead compounds [28]. In hypertension diseases ketene *N,S*-acetals derivatives used as a drug [29].

EXPERIMENTAL

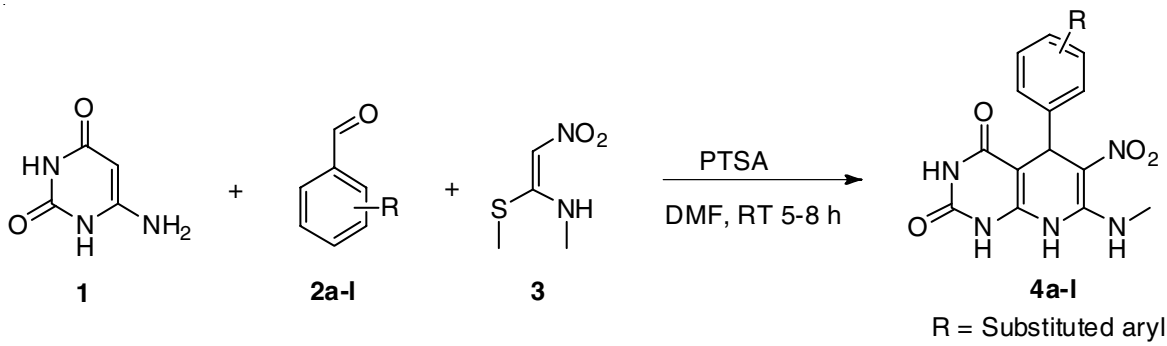
The entire reagents and solvents were used without further purification and procured from the reputed commercial sources. Reactions were monitored by thin-layer chromatography (TLC) plates. The melting points of synthesized compounds were carried out using open capillary melting point apparatus. The IR spectra were recorded on a Shimadzu FT-IR-8400 instrument using KBr. The mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in ESI (70eV) model using direct inlet probe technique and *m/z* is reported in atomic units per elementary charge. Elemental analyses were recorded on Euro vector EA3000 CHNS-O Analyzer. The NMR spectra were recorded on Brucker Avance-III 400 MHz spectrometer operating at 400 MHz (^{1}H NMR) and 101 MHz (^{13}C NMR) using DMSO-d_6 deuterated solvent and tetramethyl silane (TMS) as an internal standard.

General synthetic procedure for 7-(methylamino)-6-nitro-5-substituted aryl-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives (4a-l): The equimolar mixture of 6-amino uracil (**1**), aromatic aldehydes (**2a-l**) and *N*-methyl-1-(methylthio)-2-nitroethenamine (**3**) in DMF were added 10 mol% PTSA as a catalyst and reaction mixture was stirred at room temperature for 5-8 h. The reaction was monitored by TLC. After completion of reaction, reaction mixture was filtered under vacuum and washed with water and methanol to get desire compounds (**4a-l**) yield 74-92%.

7-(Methylamino)-6-nitro-5-phenyl-5,8-dihydropyrido-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4a): Yield: 82%; pale yellow solid; m.p.: 202-204 ºC; IR (KBr, ν_{max}, cm^{-1}): 3232.8 (N-H *str.*), 3155.65 (N-H *str.*), 2808.45 (C-H *str.*), 1712.85 (C-O *str.*), 1635.69 (C-O *str.*), 1543.1 (N-O *str.*), 1388.79 (C-H *bend.*), 1265.35 (C-N *str.* amine), 1010.73 (C=C bending monosubstituted). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.95 (s, 1H, -NH), 10.62 (s, 1H, -NH), 10.15 (br, 1H, -NH), 8.9 (br, 1H, -NH), 7.26-7.23 (dd, 2H, *J* = 8.55, 8.6 Hz, Ar), 7.02-6.98 (t, 2H, *J* = 8.6 Hz, Ar), 6.65 (t, 1H, *J* = 7.2 Hz, Ar.), 5.02 (s, 1H, -CH of pyridine ring), 3.10-3.08 (d, 3H, *J* = 5.1 Hz, -NCH$_3$). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 160.32, 158.70, 148.85, 148.26, 143.62, 128.08, 128.02, 127.54, 125.70, 125.32, 107.77, 90.23, 37.52, 29.12. Mass spectrum, *m/z* (Irel, %): 315.10 [M]$^+$; Analytical data of calcd. (found) % $C_{14}H_{13}N_5O_4$: C, 53.33 (53.30); H, 4.16 (4.18); N 22.21 (19.12).

5-(4-Fluorophenyl)-7-(methylamino)-6-nitro-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4b): Yield: 88%; pale yellow solid; m.p.: 220-222 °C; IR (KBr, ν_{max}, cm^{-1}): 3618.58 (N-H *str.*), 3448.84 (N-H *str.*), 3394.83 (N-H *str.*), 2816.16 (C-H *str.*), 1735.99 (C-O *str.*), 1512.24 (N-O *str.*), 1427.37 (C-H *bend.*), 1334.78 (C-F *str.*), 1273.06 (C-N *str.* amine), 817.85 (C-H *bend*. 1,4-disubstituted). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.97 (s, 1H, -NH), 10.64 (s, 1H, -NH), 10.21 (br, 1H, -NH), 9.05 (br, 1H, -NH), 7.28-7.24 (dd, 2H, *J* = 8.57, 8.8 Hz, Ar), 7.05-7.01 (t, 2H, *J* = 8.8 Hz, Ar), 5.04 (s, 1H, -CH of pyridine ring), 3.11-3.09 (d, 3H, *J* = 5.2 Hz, -NCH$_3$). ^{1}H NMR (400 MHz, DMSO-d_6, D$_2$O exchange, δ, ppm): 7.30-7.28 (m, 2H), 7.06-7.02 (t, 2H, *J* = 8.8 Hz), 5.05 (s, 1H), 3.11 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 161.97, 159.56, 150.49, 149.32, 141.92, 140.09, 129.52, 129.44, 114.44, 114.23, 108.36, 90.44, 36.37, 28.69. Mass spectrum, *m/z* (Irel, %): 333.09 [M]$^+$; Analytical data of calcd. (found) % $C_{14}H_{12}N_5O_4F$: C, 50.45 (50.43); H, 3.63 (3.65); N, 21.01 (21.03).

5-(4-Bromophenyl)-7-(methylamino)-6-nitro-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4c): Yield: 78%; pale yellow solid; m.p.: 218-220 ºC; IR (KBr, ν_{max}, cm^{-1}): 3340.82 (N-H *str.*), 2816.16 (C-H *str.*), 1735.99 (C-O *str.*), 1681.98 (C-O *str.*), 1543.1 (N-O *str.*), 1481.38 (C-H *bend.*), 1419.66 (C-H *bend.*), 1273.06 (C-N *str.* amine), 810.13 (C-H *bend.* 1,4-disubstituted), 555.52 (C-Br *str.*). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.99 (s, 1H, -NH), 10.65 (s, 1H, -NH), 10.23 (br, 1H, -NH), 9.09 (br, 1H, -NH), 7.32-7.29 (dd, 2H, *J* = 8.62, 9.1 Hz, Ar), 7.08-7.04 (t, 2H, *J* = 9.1 Hz, Ar), 5.08 (s, 1H, -CH of pyridine ring), 3.13-3.10 (d, 3H, *J* = 5.4 Hz, -NCH$_3$). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 161.11, 159.45, 151.21, 150.68, 140.3, 141.58, 141.62, 129.88, 129.85, 114.24, 108.36, 90.12, 36.32, 28.60. Mass spectrum, *m/z* (Irel, %): 393.01 [M]$^+$; Analytical data of calcd. (found) % $C_{14}H_{12}N_5O_4Br$: C, 42.66 (42.64); H, 3.07 (3.05); N, 17.77 (17.75).



Scheme-I: Synthetic route for compound **4a-l**

5-(4-Hydroxyphenyl)-7-(methylamino)-6-nitro-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4d): Yield: 74%; pale yellow solid; m.p.: 238-240 ºC; IR (KBr, ν_{max}, cm^{-1}): 3610.86 (O-H *str.*), 3448.84 (N-H *str.*), 3209.66 (N-H *str.*), 3047.63 (C-H *str.*), 2823.88 (C-H *str.*), 1681.98 (C-O *str.*), 1543.1 (O-H *bend.*), 1435.09 (C-H *str.*), 1334.78 (C-H *str.*), 1265.35 (C-N *str.* amine), 817.85 (C-H *bend.* 1,4-disubstituted). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.92 (s, 1H, -NH), 10.62 (s, 1H, -NH), 10.18 (br, 1H, -NH), 9.16 (s, 1H, -NH), 9.00 (s, 1H, -OH), 7.02-7.00 (d, 2H, *J* = 8.8 Hz, Ar), 6.60-6.58 (d, 2H, *J* = 8.4 Hz, Ar), 4.96 (s, 1H, -CH of pyridine ring), 3.09-3.08 (d, 3H, *J* = 5.2 Hz, -NCH_3). ^{1}H NMR (400 MHz, DMSO-d_6, D_2O exchange, δ, ppm): 7.06-7.04 (d, 2H), 6.64-6.62 (d, 2H), 4.97 (s, 1H), 3.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 161.99, 155.79, 149.37, 134.38, 128.53, 128.21, 114.41, 108.84, 91.14, 38.83, 28.65. Mass spectrum, *m/z* (Irel, %): 331.09 $[M]^+$; Analytical data of calcd. (found) % $C_{14}H_{13}N_5O_5$: C, 50.76 (50.75); H, 3.96 (3.98); N, 21.14 (21.12).

5-(3-Methoxyphenyl)-7-(methylamino)-6-nitro-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4e): Yield: 82%; pale yellow solid; m.p.: 210-212 ºC; IR (KBr, ν_{max}, cm^{-1}): 3541.42 (N-H *str.*), 3194.23 (N-H *str.*), 3132.5 (C-H *str.*), 2970.48 (C-H *str.*), 1728.28 (C-O *str.*), 1681.98 (C-O *str.*), 1643.41 (C-O *str.*), 1543.1 (N-O *str.*), 1435.09 (C-H *bend.*), 1327.07 (C-H *bend.*), 1265.35 (C-N *str.* amine), 1010.73 (C-H *bend.* 1,3-disubstituted). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.9 (s, 1H, -NH), 10.6 (s, 1H, -NH), 10.2 (s, 1H, -NH), 9.0 (s, 1H, -NH), 7.14-7.12 (d, 2H, *J* = 8.4 Hz, Ar), 6.77-6.75 (d, 2H, *J* = 8.4, Ar), 4.9 (s, 1H, -CH of pyridine ring), 3.6 (s, 3H, -OCH_3), 3.10-3.09 (d, 3H, *J* = 5.2 Hz, -NCH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 161.92, 157.60, 149.12, 136.06, 128.61, 113.10, 112.06, 108.67, 107.32, 90.92, 54.94, 35.98, 28.8. Mass spectrum, *m/z* (Irel, %): 345.11 $[M]^+$; Analytical data of calcd. (found) % $C_{15}H_{15}N_5O_5$: C, 52.17 (52.15); H, 4.38 (4.40); N, 20.28 (20.26).

5-(4-Methoxyphenyl)-7-(methylamino)-6-nitro-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4f): Yield: 92%; pale yellow solid; m.p.: 250-252 ºC; IR (KBr, ν_{max}, cm^{-1}): 3595.43 (N-H *str.*), 3487.42 (N-H *str.*), 3209.66 (N-H *str.*), 3063.06 (C-H *str.*), 2816.16 (C-H *str.*), 1689.7 (C-O *str.*), 1604.83 (C-O *str.*), 1512.24 (N-O *str.*), 1427.37 (C-H *bend.*), 1334.78 (C-H *bend.*), 1249.91 (C-N *str.* amine), 840.99 (C-H *bend.* 1,4-disubstituted). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.9 (s, 1H, -NH), 10.6 (s, 1H, -NH), 10.2 (s, 1H, -NH), 9.0 (s, 1H, -NH), 7.14-7.12 (d, 2H, *J* = 8.4 Hz, Ar), 6.77-6.75 (d, 2H, *J* = 8.4, Ar), 4.9 (s, 1H, -CH of pyridine ring), 3.68 (s, 3H, -OCH_3), 3.10-3.09 (d, 3H, *J* = 5.2 Hz, -NCH_3). ^{1}H NMR (400 MHz, DMSO-d_6, D_2O exchange, δ, ppm): 7.16-7.14 (d, 2H, *J* = 8.4 Hz), 6.79-6.77 (d, 2H, *J* = 8.8 Hz), 5.0 (s, 1H), 3.688 (s, 3H), 3.10 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 161.98, 157.74, 149.35, 136.06, 128.61, 113.10, 108.67, 90.92, 54.94, 35.98, 28.67. Mass spectrum, *m/z* (Irel, %): 345.11 $[M]^+$; Analytical data of calcd. (found) % $C_{15}H_{15}N_5O_5$: C, 52.17 (52.15); H, 4.38 (4.40); N, 20.28 (20.26).

5-(3,4-Dimethoxyphenyl)-7-(methylamino)-6-nitro-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4g): Yield: 86%; yellow solid; m.p.: 234-236 ºC; IR (KBr, ν_{max}, cm^{-1}): 3587.72 (N-H *str.*), 3495.13 (N-H *str.*), 3070.78 (C-H *str.*), 2962.76 (C-H *str.*), 1681.98 (C-O *str.*), 1512.24 (N-O *str.*), 1442.8 (C-H *bend.*), 1327.07 (C-H *bend.*), 1265.35 (C-N *str.* amine), 1141.9, 1087.89, 1018.45, 771.55, 709.83, 547.8. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.96 (s, 1H, -NH), 10.62 (s, 1H, -NH), 10.23 (s, 1H, -NH), 9.03 (s, 1H, -NH), 6.89-6.89 (d, 1H, *J* = 3.6 Hz, Ar), 6.79-6.77 (s, 1H, *J* = 8.4 Hz, Ar), 6.68-6.65 (dd, 1H, *J* = 2.0, 8.3 Hz, Ar), 5.04 (s, 1H, -CH of pyridine ring), 3.69-3.68 (d, 6H, -2OCH_3), 3.10-3.09 (d, 3H, *J* = 5.2 Hz, -NCH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 162.09, 150.65, 149.37, 147.99, 147.49, 141.83, 136.58, 119.01, 112.30, 111.57, 108.46, 90.91, 55.52, 55.48, 36.16, 28.68. Mass spectrum, *m/z* (Irel, %): 375.12 $[M]^+$; Analytical data of calcd. (found) % $C_{16}H_{17}N_5O_6$: C, 51.20 (51.15); H, 4.57 (4.59); N, 18.66 (18.62).

5-(4-(Dimethylamino)phenyl)-7-(methylamino)-6-nitro-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4h): Yield: 80%; light brown solid; m.p.: 268-270 ºC; IR (KBr, ν_{max}, cm^{-1}): 3417.98 (N-H *str.*), 3124.79 (N-H *str.*), 1689.7 (C-O *str.*), 1627.97 (C-O *str.*), 1527.67 (N-O *str.*), 1427.37 (C-H *bend.*), 1334.78 (C-H *bend.*), 1273.06 (C-N *str.* amine), 810.13 (C-H *bend*. 1,4-disubstituted). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.9 (s, 1H, -NH), 10.62 (s, 1H, -NH), 10.24 (s, 1H, -NH), 7.05-7.03 (d, 2H, *J* = 8.0 Hz, Ar), 6.61-6.59 (d, 2H, *J* = 8.4 Hz, Ar), 4.95 (s, 1H, -CH of pyridine ring), 3.09-3.08 (d, 3H, *J* = 5.2 Hz), 2.84-2.81 (br, 6H, -2×NCH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 162.01, 159.62, 151.24, 149.44, 144.72, 141.52, 138.82, 138.80, 126.52, 126.50, 108.36, 82.55, 44.12, 44.16, 38.31, 30.42. Mass spectrum, *m/z* (Irel, %): 358.14 $[M]^+$; Analytical data of calcd. (found) % $C_{16}H_{18}N_6O_4$: C, 53.63 (53.60); H, 5.06 (5.08); N, 23.45 (23.42).

7-(Methylamino)-6-nitro-5-(*p*-tolyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4i): Yield: 88%; pale yellow solid; m.p.: 210-212 ºC; IR (KBr, ν_{max}, cm^{-1}): 3379.40 (N-H *str.*), 3171.08 (N-H *str.*), 3055.35 (C-H *str.*), 2847.03 (C-H *str.*), 1720.56 (C-O *str.*), 1620.26 (C-O *str.*), 1535.39 (N-O *str.*), 1458.23 (C-H *bend.*), 1365.65 (C-H *bend.*), 1296.21 (C-N *str.* amine). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.93 (s, 1H, -NH), 10.61 (s, 1H, -NH), 10.13 (br, 1H, -NH), 8.8 (br, 1H, -NH), 6.90-6.88 (dd, 2H, *J* = 8.56, 8.70 Hz, Ar), 6.82-6.80 (t, 2H, *J* = 8.70 Hz, Ar), 5.01 (s, 1H, -CH of pyridine ring), 3.08-3.06 (d, 3H, *J* = 5.0 Hz, -NCH_3), 2.58 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 160.75, 159.62, 150.92, 149.35, 141.90, 131.21, 129.52, 129.44, 116.39, 116.36, 104.14, 92.56, 36.37, 28.69, 24.22. Mass spectrum, *m/z* (Irel, %): 329.11 $[M]^+$; Analytical data of calcd. (found) % $C_{15}H_{15}N_5O_4$: C, 54.71 (54.70); H, 4.59 (4.57); N, 21.27 (21.25).

5-(4-Chlorophenyl)-7-(methylamino)-6-nitro-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4j): Yield: 82%; pale yellow solid; m.p.: 218-220 ºC; IR (KBr, ν_{max}, cm^{-1}): 3456.55 (N-H *str.*), 3201.94 (N-H *str.*), 1681.98 (C-O *str.*), 1512.24 (N-O *str.*), 1435.09 (C-H *bend.*), 1327.07 (C-H *bend.*), 1265.35 (C-N *str.* amine), 810.13(C-H *bend*. 1,4-disubstituted), 578.66 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.98 (s, 1H, -NH), 10.64 (s, 1H, -NH), 10.22 (br, 1H, -NH), 9.07 (br, 1H, -NH), 7.31-7.30 (dd, 2H, *J* = 8.55 Hz, 8.6, Ar), 7.04-7.00 (t, 2H, *J* = 8.6 Hz, Ar), 5.06 (s, 1H, -CH of pyridine ring), 3.10-3.12 (d, 3H, *J* = 5.3 Hz, -NCH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 161.97, 159.56, 150.49, 149.32, 140.09, 140.06, 129.44, 114.44, 108.36, 90.44, 36.37, 28.69. Mass spectrum, *m/z* (Irel, %): 349.06 $[M]^+$; Analytical data of

calcd. (found) % $C_{14}H_{12}N_5O_4Cl$: C, 48.08 (48.05); H, 3.46 (3.44); N, 20.03 (20.05).

7-(Methylamino)-6-nitro-5-(4-nitrophenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4k): Yield: 78%; pale yellow solid; m.p.: 230-232 ºC; IR (KBr, ν_{max}, cm^{-1}): 3417.98 (N-H *str.*), 3124.79 (N-H *str.*), 2978.19, 1689.7 (C-O *str.*), 1519.96 (N-O *str.*), 1427.37 (C-H bending), 1334.78 (C-H *bend.*), 1273.06 (C-N *str.* amine), 810.13 (C-H *bend.* 1,4-disubstituted). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.99 (s, 1H, -NH), 10.66 (s, 1H, -NH), 10.22 (br, 1H, -NH), 9.08 (br, 1H, -NH), 7.32-7.29 (dd, 2H, *J* = 8.62, 9.1 Hz, Ar), 7.08-7.04 (t, 2H, *J* = 9.1 Hz, Ar), 5.08 (s, 1H, -CH of pyridine ring), 3.12-3.10 (d, 3H, *J* = 5.4 Hz, -NCH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 161.82, 159.72, 150.92, 149.66, 142.74, 141.76, 140.31, 129.99, 128.12, 122.68, 114.23, 90.42, 36.30, 28.65. Mass spectrum, *m/z* (Irel, %): 360.08 $[M]^+$; Analytical data of calcd. (found) % $C_{14}H_{12}N_6O_6$: C, 46.67 (46.69); H, 3.36 (3.34); N, 23.33 (23.35).

5-(Furan-2-yl)-7-(methylamino)-6-nitro-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4l): Yield: 76%; yellow solid; m.p.: 244-246 ºC; IR (KBr, ν_{max}, cm^{-1}): 3387.11 (N-H *str.*), 3171.08 (N-H *str.*), 3055.35, 2839.31, 1712.85, 1620.26 (C-O *str.*), 1535.39 (N-O *str.*), 1458.23 (C-H *bend.*), 1365.65 (C-H *bend.*), 1288.49 (C-N *str.* amine). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.94 (s, 1H, -NH), 10.60 (s, 1H, -NH), 10.12 (br, 1H, -NH), 8.8 (br, 1H, -NH), 7.4 (d, 1H, *J* = 5.8 Hz, Ar.), 7.2 (d, 1H, *J* = 5.6 Hz, Ar.), 6.4 (t, 1H, *J* = 5.0, Ar.), 4.78 (s, 1H, -CH of pyridine ring), 3.10-3.08 (d, 3H, *J* = 5.2 Hz, -NCH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δ, ppm): 160.66, 158.32, 150.47, 149.32, 142.92, 141.04, 112.38, 108.42, 104.88, 90.32, 36.37, 28.69. Mass spectrum, *m/z* (Irel, %): 305.08 $[M]^+$; Analytical data of calcd. (found) % $C_{12}H_{11}N_5O_5$: C, 47.22 (47.24); H, 3.63 (3.65); N, 22.94 (22.90).

RESULTS AND DISCUSSION

Initially, the synthesis of 5-aryl-7-methylamino-6-nitro-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione compounds using 6-amino uracil, substituted aldehyde and *N*-methyl-1-(methylthio)-2-nitroethen-1-amine in DMF and PTSA as a catalyst was examined. Based on some limited study to establish an effective, mild and rapid reaction for the synthesis of pyrido[2,3-*d*]pyrimidine, initially we performed a reaction in polar solvents such as methanol, ethanol, water and DMF at various temperatures and in the presence of different catalyst such as PTSA, sulfamic acid, acetic acid and HCl (Table-1). Based on Table-1 results, it is clear the PTSA as catalyst and DMF as solvent gives a high percentage of yield. Then, the same reaction was performed using various amount of PTSA (Table-1, entry 7 and 10), however, 10 mol% PTSA exhibit the best result (Table-1, entry 7).

All the newly synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry analysis. In particular ^{1}H NMR spectrum of desire compounds, all –NH peak in deshielded region around 10.9 δ ppm to 9.0 δ ppm were observed. In the deuterated exchange NMR, all –NH peak were disappeared from the deshielded region. In ^{1}H NMR, the aromatic proton has shown in region 6.5-7.3 δ ppm. The chiral proton (-CH of pyridine ring) shown singlet peak around 4.9 to 5.0 δ ppm. In compound **4d**, the –OH peak observed in deshielded region at 8.7 δ ppm and also this phenolic proton disappear in deuterated exchange. In the shielded region, the –NCH_3 exhibited the doublet peak around 3.08 δ ppm. In the compound **4f**, the methoxy peak observed at 3.68 δ ppm, in compound **4g** the both methoxy observed at 3.68 and 3.69 δ ppm and compound **4h** the –$N(CH_3)_2$ the both methyl peak observed at 2.84 δ ppm. In particular ^{13}C NMR, we observed the both C=O (pyrimidine ring) peak in deshielded region around 161 to 158 δ ppm and the N-C-N urea linkage peak observed in the range of 149-150 δ ppm. The all aromatic carbon peak observed in the range of 90-138 δ ppm, the chiral carbon (-CH) of pyridine ring exhibited a peak around 38 δ ppm and the –NCH_3 methyl peak appeared around 28 δ ppm.

In particular FT-IR data, the amidic N-H stretching in the range of 3610-3200 cm^{-1} and the aryl C-H stretching at around 3124-3060 cm^{-1} were observed. In alkane C-H stretching peak was observed at 2870-2816 cm^{-1},whereas the C=O of amidic appeared at 1735-1635 cm^{-1}. The N-O stretching peak in the all mono, 1,3- and 1,4-disubstituted compounds was observed around 1543-1512 cm^{-1}, whereas the C-H bending appeared at 1427-1387 cm^{-1} also observed. In the mass spectrometry, the M-2 peak was observed in all the synthesized compound, which is attributed due to the removal of two hydrogen in EI method, also the M-30 peak of removal of –NCH_3 and nitro group peak in mass spectrometry were observed. In LC-MS, the M+1 peak also in the ^{1}H NMR spectrum was observed, moreover, the –CH peak of dihydropyridine ring and in the ^{13}C NMR spectrum, the carbon was shown in the shielded region, which clear the synthesized compounds have a sp^3 carbon. Thus, it is clear that all the synthesized compounds contain a dihydropyridine ring not a unsaturated pyridine ring.

TABLE-1
REACTION OPTIMIZATION DATA OF COMPOUND **4f**

Solvent	Catalyst	Temperature (°C)	Time (h)	Yield (%)
EtOH	PTSA	RT	12	10
EtOH	PTSA	80	4	35
Water	PTSA	RT	10	25
EtOH	Sulfamic acid	80	6	45
DMF	PTSA	120	15 min in MW	35
DMF	PTSA	80	3	45
DMF	PTSA (10 mol%)	RT	8	92
DMF	Sulfamic acid	RT	10	65
DMF	HCl	RT	6	70
DMF	PTSA (5 mol%)	RT	12	60
DMF	AcOH	RT	15	45

TABLE-2
ANTIMICROBIAL ACTIVITY DATA OF SYNTHESIZED COMPOUNDS **4a-l**

Entry	Minimum inhibitory concentration (µg/mL)					
	Antibacterial activity				Antifungal activity	
	Gram-positive bacteria		Gram-negative bacteria			
	S. aureus	*B. subtillis*	*E. coli*	*S. typhi*	*A. niger*	*A. clavatus*
4a	200	250	200	250	250	350
4b	100	125	150	100	100	300
4c	250	300	125	175	250	300
4d	250	250	200	250	200	250
4e	125	100	200	150	250	200
4f	300	250	350	300	250	100
4g	250	350	300	400	250	250
4h	325	200	500	350	500	350
4i	225	200	250	200	200	125
4j	100	200	500	300	>1000	500
4k	400	250	200	100	350	400
4l	150	200	250	300	200	250
Ampicillin	250	250	100	100	–	–
Chloramphenicol	50	50	50	50	–	–
Ciprofloxacin	50	50	25	25	–	–
Norfloxacin	10	100	10	10	–	–
Nystatin	–	–	–	–	100	100
Griseofulvin	–	–	–	–	100	100

Antimicrobial activity: The antimicrobial activities of the synthesized compounds **4a-l** were determined by Micro Broth Dilution method and the compounds were screend against various bacterial pathogens *viz*. *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 441), *Escherichia coli* (MTCC 443), *Salmonella typhi* (MTCC 98), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323). Ampicillin, chloramphenicol, ciprofloxacin, norfloxacin were used as the positive control against bacterial species, whereas nystatin and griseofulvin were used as fungal species. Dimethyl sulfoxide was used as solvent control.

The MIC values of all the synthesized compounds **4a-l** are shown in Table-2. Among all the synthesized compounds, **4b**, **4e** and **4j** exhibits moderate inhibition against Gram-positive bacterial species. Compounds **4b** and **4e** against *S. aureus, B. subtillis* and compound **4j** against *S. aureus* species. Compounds **4a**, **4c** and **4k** show moderate inhibition against *S. typhi, E. coli* and *S. typhi* species, respectively. In antifungal activities good inhibition exhibited by compound **4a** against *A. niger* while compounds **4f** and **4i** exhibit against *A. clavatus* species.

Conclusion

The synthesis of new derivatives of dihydropyrido[2,3-*d*]-pyrimidine *via* one-pot three component reaction of 6-amino uracil, substituted aryl aldehydes and *N*-methyl-1-(methyl-thio)-2-nitroethenamine in the presence of PTSA 10 mol% as a catalyst was successfully, effectively in high yield acheived. Most of the synthesized compounds show moderate to good activity. Out of all the compounds, **4b** having flouro substitution exhibited good inhibition compared with standard drug.

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