Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(7):148-156
(http://derpharmachemica.com/archive.html)

$Al(DS)_3$ Catalyzed, One-pot Synthesis and Antibacterial Studies of tetra substituted 1,4-Dihydropyridines in Aqueous Media

Harvinder Singh Sohal [1,*], Manvinder Kaur[2], Anu Radha Thakur[1] and Priyanka Parmar[1]

[1]*Department of Chemistry, Chandigarh University, Ghauran-140 413, Punjab, India*
[2]*Department of Chemistry, Punjabi University, Patiala-147 001, Punjab, India*

ABSTRACT

Multi component, one pot synthesis of tetra substituted 1,4-dihydropyridine derivatives from the condensation of barbituric acid, methyl acetoacetate, aromatic aldehyde and ammonium acetate has been demonstrated using an highly efficient catalyst Aluminium tris(dodecyl sulphate) ($Al(DS)_3$) in aqueous medium. The synthesized molecules were obtained in excellent yield and high purity without use of any additional methodology. Further, the synthesized compounds were found to exhibit potent antibacterial activity against various gram positive and gram negative bacterial strains as compared with the standard antibiotic drug (Amoxicillin).

Keywords: $Al(DS)_3$, Barbituric Acid, 1,4-Dihydropyridine, Antibacterial Activity

---

INTRODUCTION

Multi-component reactions (MCRs) are special type of naturally useful organic reactions in which three or more different starting materials react to yield final product in a one-pot procedure [1]. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated, and high throughput generation of organic compounds [2]. The discovery of novel MCRs can be considered as an interesting topic for academic research that also satisfies a practical interest of applied science.

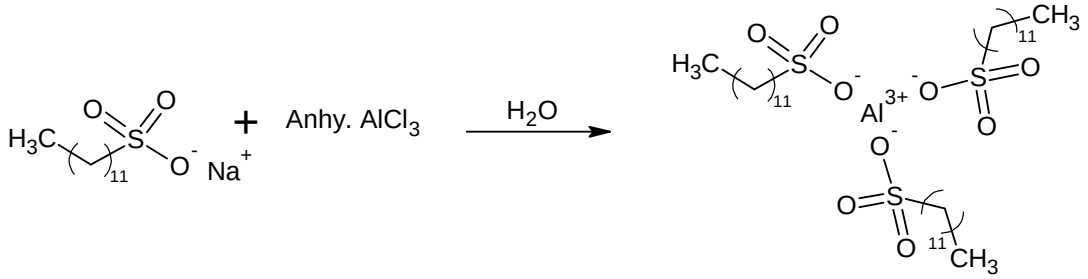
1,4-dihydropyridines (1,4-DHP's) found birth with MCRs in 1882 with Hantzsch condensation [3]. 1,4-DHP's attracted more attention because of its presence in the coenzyme, diphosphopyridine nucleotide (DPNH) [4] and identification as bio-active material. The activity profiles of 1,4-DHP's were further expanded as they were detected to possess anti-tumor [5], anti-inflammatory [6], anticonvulsant activity [7], anti-tubercular activity [8, 9] cerebral anti-schemic activity in the treatment of Alzheimer's disease, PAF-acether antagonists [10], *etc*. Invention and execution of various new methodologies have engendered for the synthesis of substituted 1,4-DHP's. Recently organic reactions in water without use of harmful organic solvents have attracted much attention because water is an abundant, safe, environmentally benign solvent [11] which virtually cost nothing. However water based processes are still subject to limitations due to solubility problems of highly hydrophobic substrates. So it is necessary to add some phase-transfer catalyst (PTC) or surfactant such as hexadecyltrimethylammonium bromide [12] (HTMAB), tetrabutylammonium bromide [13] (TBAB), *p*-dodecylbenesulfonic acid [14] (DBSA) and Sodium dodecylsulphate [15] (SDS) because during synthesis they promote the uniform dispersion of organic materials in water. Keeping the above in mind a surfactant based Aluminium tris(dodecyl sulphate) [16] $Al(DS)_3$ as catalyst (Scheme 1) is brought into use. Persisting with our work on hetrocyclics [17], $Al(DS)_3$ found to be an efficient catalyst for the synthesis of tetra-substituted 1,4-dihydropyridines (Scheme 2).

MATERIALS AND METHODS

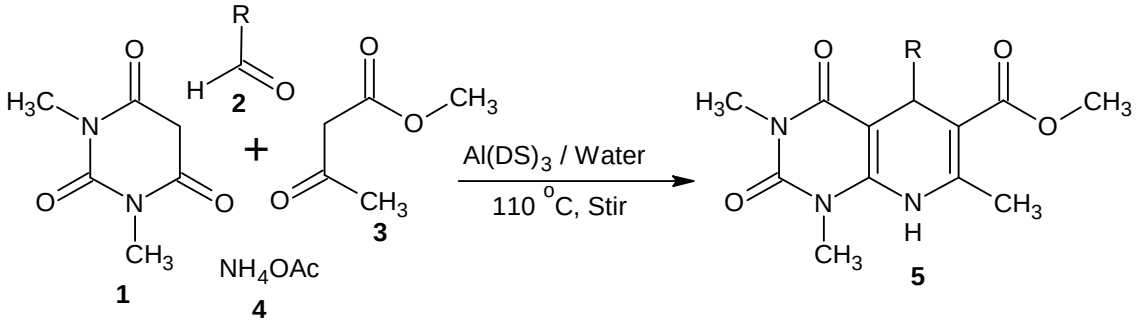
General

Materials were obtained from commercial suppliers and were used without further purifications. Melting points were recorded in open end capillaries and are uncorrected. ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Bruker Avance II 400 MHz spectrometer; chemical shifts (δ) are reported in ppm relative to TMS as internal standard. The mass spectrum and IR spectra were recorded at LC-MS Spectrometer Model Q-ToF Micro Waters and Perkin-Elmer Spectrum II infra-red spectrophotometer, respectively. Elemental analyses (C, H, and N) were performed using a Thermo Scientific elemental analyzer. Chemicals were purchased from local suppliers and used without further purification. The reactions were monitored on thin layer chromatography (TLC) using silica gel-G. The spots were visualized by using iodine vapours.

Synthesis of Aluminium tris(dodecyl sulphate) ($Al(DS)_3$): In two separated beakers dissolve Anhy. $AlCl_3$ (0.1 mol) and Sodium dodecylsulphate (SDS) (0.3 mol) in minimum quantity of water. Mix both the solutions drop-wise with constant stirring at room temperature, a colourless solid separated out, filter it to afford solid $Al(DS)_3$.



Scheme 1: Synthesis of Aluminium tris(dodecyl sulphate) $Al(DS)_3$



Scheme 2: Synthesis of tetra substituted 1,4-dihydropyridines using 3 mol% $Al(DS)_3$

Synthesis of Methyl-1,3,7-trimethyl-5-phenyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate 5a

In a conical flask benzaldehyde (0.01 mol), methyl acetoacetate (0.01 mol), barbituric acid (0.01 mol) and ammonium acetate (0.02 mol) were taken in aqueous solution (10 ml) containing $Al(DS)_3$ (3 mol%) and stirred at 110 ^{o}C for the stipulated time (Table 1). After the completion of reaction (monitored by TLC), reaction mixture was cooled to room temperature and added 50 ml ice-cold water, solid separated out. Extract the product from ethyl acetate, upon evaporation under reduced pressure crude product is obtained. Recrystalised from ethanol to afford compound **5a**.Yield 91%; m.p. 289-290 ^{o}C; IR (KBr): ν_{max} cm^{-1} 3342 (N-H Str.), 1732 (C=O Str.), 1710 (C=O Str.), 1689 (C=O Str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39-7.14 (m, 5H, Ar-***H***), 6.03 (s, 1H, N***H***), 5.04 (s, 1H, C***H***), 3.93 (s, 3H, COOC***H***$_3$), 3.43 (s, 3H, NC***H***$_3$), 3.24 (s, 3H, NC***H***$_3$), 2.13 (s, 3H, C***H***$_3$); MS *m/z* 342 (M^+); Anal. Calc. for $C_{18}H_{19}N_3O_4$: Calc. C, 63.33%, H, 5.61%, N, 12.31%; Found: C, 63.32%, H, 6.59%, N, 12.30%.

Methyl-1,3,7-trimethyl-5-(4-methylphenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylate (5b). Yield 83%; m.p. 287-288 ^{o}C; IR (KBr) ν_{max} cm^{-1} 3335 (N-H Str.), 1729 (C=O Str.), 1708 (C=O Str.), 1688 (C=O Str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31-7.10 (m, 4H, Ar-***H***), 6.01 (s, 1H, N***H***), 5.02 (s, 1H,

C***H***), 3.89 (s, 3H, COOC***H***$_3$), 3.39 (s, 3H, NC***H***$_3$), 3.20 (s, 3H, NC***H***$_3$), 2.12 (s, 3H, C***H***$_3$), 2.09 (s, 3H, C***H***$_3$); MS *m/z* 356 (M^+); Anal. Calc. for $C_{19}H_{21}N_3O_4$: Calc. C, 64.21%, H, 5.96%, N, 11.82%; Found: C, 64.19%, H, 5.95%, N, 11.82%.

Methyl-1,3,7-trimethyl-5-(3,4-dimethylphenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido [2,3-d] pyrimidine-6-carboxylate (5c). Yield 85%; m.p. 270-2972 ^oC; IR (KBr) ν_{max} cm^{-1} 3329 (N-H Str.), 1726 (C=O Str.), 1707 (C=O Str.), 1689 (C=O Str.); ^1H NMR (400 MHz, DMSO-d_6): δ 7.31-7.06 (m, 3H, Ar-***H***), 5.99 (s, 1H, N***H***), 5.02 (s, 1H, C***H***), 3.86 (s, 3H, COOC***H***$_3$), 3.38 (s, 3H, NC***H***$_3$), 3.16 (s, 3H, NC***H***$_3$), 2.11 (s, 3H, C***H***$_3$), 2.04 (s, 3H, C***H***$_3$), 1.99 (s, 3H, C***H***$_3$); MS *m/z* 370 (M^+); Anal. Calc. for $C_{20}H_{23}N_3O_4$: Calc. C, 65.03%, H, 6.28%, N, 11.37%; Found: C, 65.01%, H, 6.25%, N, 11.35%.

Methyl-1,3,7-trimethyl-5-(4-florophenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate (5d). Yield 82%; m.p. 260-261 ^oC; IR (KBr) ν_{max} cm^{-1} 3336 (N-H Str.), 1733 (C=O Str.), 1712 (C=O Str.), 1691 (C=O Str.); ^1H NMR (400 MHz, DMSO-d_6): δ 7.39-7.18 (m, 4H, Ar-***H***), 6.12 (s, 1H, N***H***), 5.06 (s, 1H, C***H***), 3.94 (s, 3H, COOC***H***$_3$), 3.45 (s, 3H, NC***H***$_3$), 3.26 (s, 3H, NC***H***$_3$), 2.13 (s, 3H, C***H***$_3$); MS *m/z* 360 (M^+); Anal. Calc. for $C_{18}H_{18}FN_3O_4$: Calc. C, 60.16%, H, 5.05%, N, 11.69%; Found: C, 60.15%, H, 5.02%, N, 11.68%.

Methyl-1,3,7-trimethyl-5-(4-chlorophenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate (5e). Yield 86%; m.p. 244-246 ^oC; IR (KBr) ν_{max} cm^{-1} 3338 (N-H Str.), 1734 (C=O Str.), 1713 (C=O Str.), 1692 (C=O Str.); ^1H NMR (400 MHz, DMSO-d_6): δ 7.40-7.15 (m, 4H, Ar-***H***), 6.10 (s, 1H, N***H***), 5.05 (s, 1H, C***H***), 3.93 (s, 3H, COOC***H***$_3$), 3.44 (s, 3H, NC***H***$_3$), 3.26 (s, 3H, NC***H***$_3$), 2.14 (s, 3H, C***H***$_3$); MS *m/z* 376 (M^+); Anal. Calc. for $C_{18}H_{18}ClN_3O_4$: Calc. C, 57.53%, H, 4.83%, N, 11.18%. Found: C, 57.52%, H, 4.81%, N, 11.17%.

Methyl-1,3,7-trimethyl-5-(3,4-dichlorophenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido [2,3-d]pyrimidine-6-carboxylate (5f). Yield 81%; m.p. 252-257 ^oC; IR (KBr) ν_{max} cm^{-1} 3340 (N-H Str.), 1731 (C=O Str.), 1713 (C=O Str.), 1694 (C=O Str.); ^1H NMR (400 MHz, DMSO-d_6): δ 7.44-7.20 (m, 3H, Ar-***H***), 6.14 (s, 1H, N***H***), 5.09 (s, 1H, C***H***), 3.95 (s, 3H, COOC***H***$_3$), 3.51 (s, 3H, NC***H***$_3$), 3.32 (s, 3H, NC***H***$_3$), 2.17 (s, 3H, C***H***$_3$); MS *m/z* 411 (M^+); Anal. Calc. for $C_{18}H_{17}Cl_2N_3O_4$: Calc. C, 52.70%, H, 4.18%, N, 10.24%; Found: C, 52.68%, H, 4.17%, N, 10.23%.

Methyl-1,3,7-trimethyl-5-(3-nitrophenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate (5g). Yield 89%; m.p. 288-290 ^oC; IR (KBr) ν_{max} cm^{-1} 3361 (N-H Str.), 1743 (C=O Str.), 1721 (C=O Str.), 1701 (C=O Str.); ^1H NMR (400 MHz, DMSO-d_6): δ 7.60-7.86 (m, 4H, Ar-***H***), 6.23 (s, 1H, N***H***), 5.44 (s, 1H, C***H***), 4.01 (s, 3H, COOC***H***$_3$), 3.62 (s, 3H, NC***H***$_3$), 3.41 (s, 3H, NC***H***$_3$), 2.29 (s, 3H, C***H***$_3$); MS *m/z* 387 (M^+); Anal. Calc. for $C_{18}H_{18}N_4O_6$: Calc. C, 55.96%, H, 4.70%, N, 14.50%; Found: C, 55.95%, H, 4.69%, N, 14.50%.

Methyl-1,3,7-trimethyl-5-(4-nitrophenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate (5h). Yield 91%; m.p. 297-299 ^oC; IR (KBr) ν_{max} cm^{-1} 3372 (N-H Str.), 1744 (C=O Str.), 1724 (C=O Str.), 1703 (C=O Str.); ^1H NMR (400 MHz, DMSO-d_6): δ 8.21-7.65 (m, 4H, Ar-***H***), 6.37 (s, 1H, N***H***), 5.54 (s, 1H, C***H***), 4.08 (s, 3H, COOC***H***$_3$), 3.67 (s, 3H, NC***H***$_3$), 3.43 (s, 3H, NC***H***$_3$), 2.31 (s, 3H, C***H***$_3$); MS *m/z* 387 (M^+);Anal. Calc. for $C_{18}H_{18}N_4O_6$: Calc. C, 55.96%, H, 4.70%, N, 14.50%; Found: C, 55.95% H, 4.68%, N, 14.47%.

Methyl-1,3,7-trimethyl-5-(3-methoxyphenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate (5i). Yield 83%; m.p. 267-268 ^oC; IR (KBr) ν_{max} cm^{-1} 3351 (N-H Str.), 1728 (C=O Str.), 1712 (C=O Str.), 1693 (C=O Str.); ^1H NMR (400 MHz, DMSO-d_6): δ 7.32-6.95 (m, 4H, Ar-***H***), 6.02 (s, 1H, N***H***), 5.01 (s, 1H, C***H***), 3.91 (s, 3H, COOC***H***$_3$), 3.89 (s, 3H, OC***H***$_3$), 3.41 (s, 3H, NC***H***$_3$), 3.26 (s, 3H, NC***H***$_3$), 2.06 (s, 3H, C***H***$_3$); MS *m/z* 372 (M^+); Anal. Calc. for $C_{19}H_{21}N_3O_5$: Calc. C, 61.45%, H, 5.70%, N, 11.31%; Found: C, 61.43%, H, 5.67%, N, 11.31%.

Methyl-1,3,7-trimethyl-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate (5j) Yield 84%; m.p. 267-269 ^oC; IR (KBr) ν_{max} cm^{-1} 3349 (N-H Str.), 1725 (C=O Str.), 1709 (C=O Str.), 1691 (C=O Str.); ^1H NMR (400 MHz, DMSO-d_6): δ 7.36-6.90 (m, 4H, Ar-***H***), 5.99 (s, 1H, N***H***), 4.98 (s, 1H, C***H***), 3.88 (s, 3H, COOC***H***$_3$), 3.79 (s, 3H, OC***H***$_3$), 3.39 (s, 3H, NC***H***$_3$), 3.21 (s, 3H, NC***H***$_3$), 2.02 (s, 3H, C***H***$_3$); MS *m/z* 372 (M^+); Anal. Calc. for $C_{19}H_{21}N_3O_5$: Calc. C, 61.45%, H, 5.70%, N, 11.31%; Found: C, 61.44%, H, 5.67%, N, 11.30%.

Methyl-1,3,7-trimethyl-5-(3,4-dimethoxyphenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido [2,3-d]pyrimidine-6-carboxylate (5k) Yield 81%; m.p. 275-276 ^{o}C; IR (KBr) ν_{max} cm^{-1} 3346 (N-H Str.), 1719 (C=O Str.), 1705 (C=O Str.), 1688 (C=O Str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.11-6.71 (m, 3H, Ar-***H***), 5.92 (s, 1H, N***H***), 4.94 (s, 1H, C***H***), 3.87 (s, 3H, COOC***H***$_3$), 3.81 (s, 3H, OC***H***$_3$), 3.73 (s, 3H, OC***H***$_3$), 3.31 (s, 3H, NC***H***$_3$), 3.17 (s, 3H, NC***H***$_3$), 2.0 (s, 3H, C***H***$_3$); MS *m/z* 402 (M$^+$); Anal. Calc. for $C_{20}H_{23}N_3O_6$: Calc. C, 59.84%, H, 5.78%, N, 10.47%; Found: C, 59.84%, H, 5.77%, N, 10.45%.

Methyl-1,3,7-trimethyl-5-(3,4,5-trimethoxyphenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydro pyrido[2,3-d]pyrimidine-6-carboxylate (5l). Yield 77%; m.p. 270-272 ^{o}C; IR (KBr) ν_{max} cm^{-1} 3341 (N-H Str.), 1714 (C=O Str.), 1701 (C=O Str.), 1684 (C=O Str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.92 (s, 2H, Ar-***H***), 5.90 (s, 1H, N***H***), 4.96 (s, 1H, C***H***), 3.89 (s, 3H, OC***H***$_3$), 3.87(s, 3H, OC***H***$_3$), 3.81 (s, 3H, COOC***H***$_3$), 3.76 (s, 3H, OC***H***$_3$), 3.33 (s, 3H, NC***H***$_3$), 3.16 (s, 3H, NC***H***$_3$), 2.07 (s, 3H, C***H***$_3$); MS *m/z* 432 (M$^+$); Anal. Calc. for $C_{21}H_{25}N_3O_7$: Calc. C, 58.46%, H, 5.84%, N, 9.74%; Found: C, 58.45%, H, 5.81%, N, 9.72%.

Methyl-1,3,7-trimethyl-5-(4-hydroxyphenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate (5m). Yield 82%; m.p. 244-246 ^{o}C; IR (KBr) ν_{max} cm^{-1} 3502 (O-H Str.), 3345 (N-H Str.), 1724 (C=O Str.), 1707 (C=O Str.), 1693 (C=O Str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.93 (s, 1H, OH), 7.31-7.06 (m, 4H, Ar-***H***), 6.04 (s, 1H, N***H***), 5.08 (s, 1H, C***H***), 3.96 (s, 3H, COOC***H***$_3$), 3.42 (s, 3H, NC***H***$_3$), 3.27 (s, 3H, NC***H***$_3$), 2.18 (s, 3H, C***H***$_3$); MS *m/z* 358 (M$^+$); Anal. Calc. for $C_{18}H_{19}N_3O_5$: Calc. C, 60.50%, H, 5.36%, N, 11.76%; Found: C, 60.48%, H, 5.36%, N, 11.74%.

Methyl-1,3,7-trimethyl-5-(2-furyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylate (5n). Yield 77%; m.p. 299-300 ^{o}C; IR (KBr) ν_{max} cm^{-1} 3346 (N-H Str.), 1731 (C=O Str.), 1714 (C=O Str.), 1697 (C=O Str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29-6.99 (m, 3H, Furyl-***H***), 6.06 (s, 1H, N***H***), 5.06 (s, 1H, C***H***), 3.95 (s, 3H, COOC***H***$_3$), 3.39 (s, 3H, NC***H***$_3$), 3.24 (s, 3H, NC***H***$_3$), 2.15 (s, 3H, C***H***$_3$); MS *m/z* 332 (M$^+$); Anal. Calc. for $C_{16}H_{17}N_3O_5$: Calc. C, 58.00%, H, 5.17%, N, 12.68%; Found: C, 57.97%, H, 5.16% N, 12.66%.

Antimicrobial evaluation

The cultures required for the biological study of compounds **5a-5n** were obtained from MTCC (Microbial Type Culture Collection & Gene Bank, Chandigarh-160036, India). The *in vitro* antibacterial activity of all the synthesized compounds **5a-5n** were evaluated against six bacterial strains (both gram positive and gram negative bacteria) *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 441), *Streptococcus pyogenes* (MTCC 442), *Escherichia coli* (MTCC 443), *Klebsellia pneumonia* (MTCC 3384) and *Pseudomonas aeruginosa* (MTCC 424).

Minimum Inhibition Concentration (MIC) of all the synthesized compounds **5a-5n** was evaluated with help of serial tube dilution method [18] at several concentrations of 128, 64, 32, 16, 8, 4 μg/ml and all the stock solutions were prepared in DMSO by dissolving weighed amounts of compounds. Dilutions were made in nutrient broth medium to prepare various concentrations. Standard drug amoxicillin was used to evaluate MIC of the prepared compounds against the tested bacterial strains. All the bacterial strains were grown in nutrient broth media at 37˚C. The inoculated tubes were incubated for 24 hrs at 37˚C. The reference drug was also sustained at the similar conditions for comparison. The inhibition of the bacterial growth was determined by the appearance of turbidity after 24 hrs of incubation at 37^{o}C. The zone of inhibition of title compounds **5a-5n** was also determined by using paper disc diffusion method. The zone of inhibitions (*mm*) has been recorded as the average diameters and MIC of all the compounds are given in **Table 4**.

RESULTS AND DISCUSSION

Chemistry

Condensation of barbituric acid, benzaldehyde, methyl acetoacetate and ammonium acetate were carried out using varying amounts of $Al(DS)_3$ in aqueous medium at different temperatures. It was found that 3 mol% catalyst (Entry 3, Table 1) at 110 ^{o}C (Entry 5, Table 2)enough to catalyze the reaction. Further ascend the amount of catalyst will not affect the rate of reaction but further increase in temperature result in the decomposition of the reaction mixture.

Table 1: Efficacy of catalyst on the synthesis of 1,4DHPs at 100 °C

Entry	Amount of catalyst	(mol %)	Compound	Time (hr)	Yield[a] (%)
1	1		5a	10	73
2	2		5a	7	77
3	3		5a	5	94
4	4		5a	5	94
5	5		5a	4.5	94

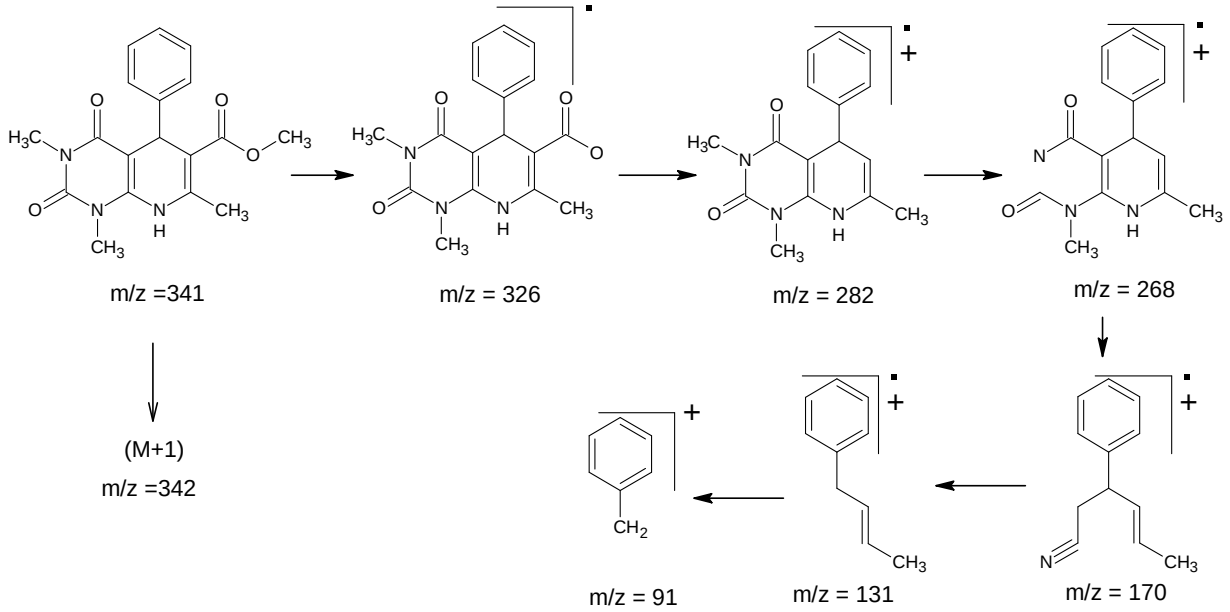
[a]*Yield refer to combined amounts of different crops.*

Table 2: Effect of temperature on the synthesis of 1,4-DHPs using 3 mol% catalyst.

Entry	Temperature[a] (°C)	Compound	Time (hr)	Yield[b] (%)
1	70	5a	18	40
2	80	5a	11	59
3	90	5a	5	88
4	100	5a	5	94
5	110	5a	3	94
6	120	5a	3	93

[a]*Reaction carried in oil bath and temperature is controlled with thermometer.*
[b]*Yield refer to combined amounts of different crops.*

The structure of the compound **5a** was confirmed with the help of spectral techniques. In IR spectrum absorption at 3342 cm^{-1} represents the N-H stretching and absorption for three C=O groups were observed at 1732, 1710 and 1689 cm^{-1}. In ^1H NMR spectrum peaks for five aromatic protons are observed at δ 7.39-7.14, singlet at δ 5.04 for C***H*** proton, singlet at δ 6.03 for N***H*** proton and singlet for two NC$\boldsymbol{H}_3$ groups observed at δ 3.43 and δ 3.24. Two singlet's for C$\boldsymbol{H}_3$ and COOC$\boldsymbol{H}_3$ group observed at δ 2.13 and δ 3.93. ESI-MS spectrum of **5a** was also helpful to interpret its structure whose mass fragmentation shown in Scheme-3 and Figure 1. Spectral data of **5a** fully supports the structure assigned to it.



Scheme-3: Mass fragmentation of Methyl-1,3,7-trimethyl-5-phenyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylate 5a

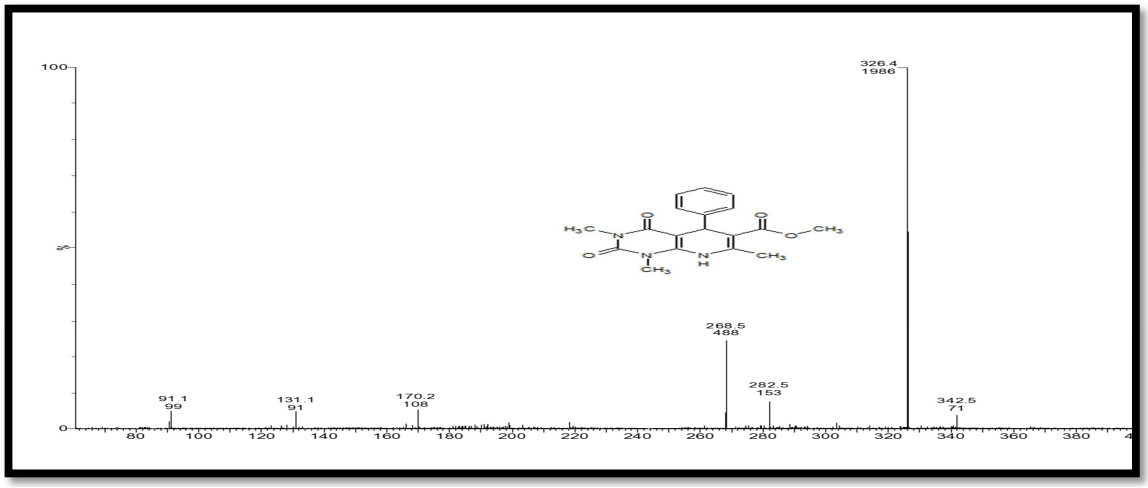


Figure 1: Mass spectrum of Methyl-1,3,7-trimethyl-5-phenyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylate 5a

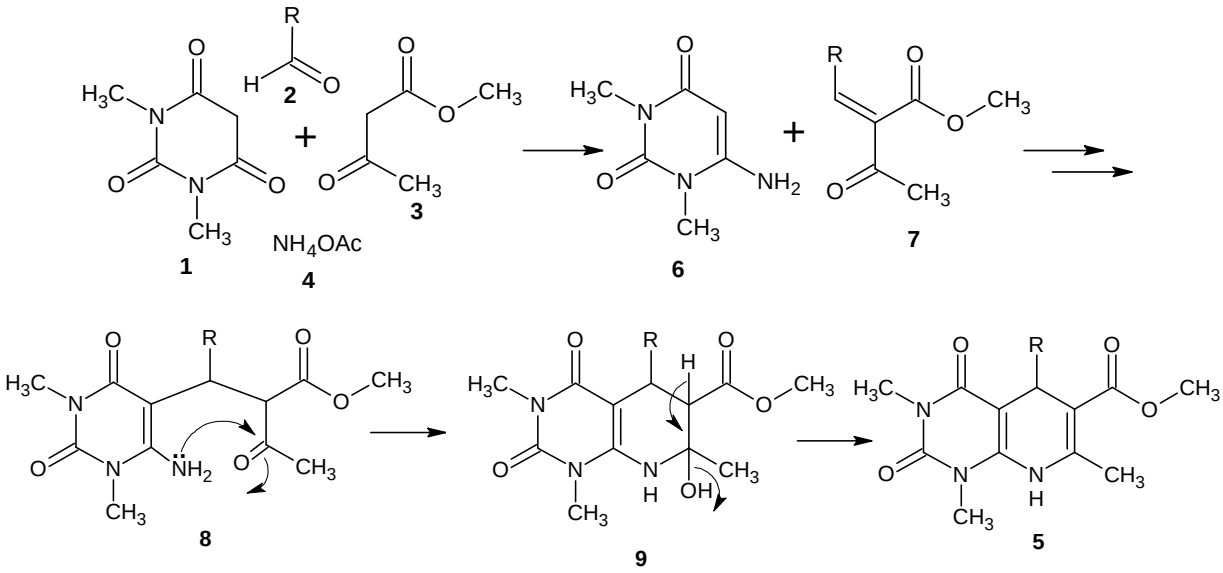
Similarly, other Methyl-1,3,7-trimethyl-5-aryl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylate**, 5b-5n** have been synthesised by the condensation of methyl acetoacetate **3**, aldehyde **2,** barbituric acid **1** and ammonium acetate **4** in aqueous solution containing $Al(DS)_3$. The results are summarized in **Table 3**.

Table 3: Synthesis of tetra-substituted 1,4-dihydropyridines from barbituric acid, methyl acetoacetate, aldehyde and ammonium acetate using $Al(DS)_3$ 3 mol% catalyst

Entry	Aldehyde (R)	Yield[a] (%)	Melting Point (^oC)	R_f value[d]
5a	C_6H_5	91	289-290	0.77
5b	4-Me C_6H_4	83	287-288	0.63
5c	3,4-Me C_6H_3	85	270-272	0.58
5d	4-F C_6H_4	82	260-261	0.68
5e	4-Cl C_6H_4	86	244-246	0.71
5f	3,4-Cl C_6H_4	81	252-257	0.72
5g	3-NO_2 C_6H_4	89	288-290	0.76
5h	4-NO_2 C_6H_4	91	297-299	0.77
5i	3-OMe C_6H_4	83	267-268	0.62
5j	4-OMe C_6H_4	84	267-269	0.63
5k	3,4-OMe C_6H_3	81	275-276	0.67
5l	3,4,5-OMe C_6H_2	77	270-272	0.59
5m	4-OH C_6H_4	82	244-246	0.74
5n	2-Furyl	77	299-300	0.58

[a] *Yield refer to combined yield of different crops*
[b] *Reactions were carried out in silicon oil bath and temperature was controlled using thermometer*
[c] *Product obtained were characterized using latest spectroscopic techniques.*

Reactions proceed smoothly with aldehydes carrying electron withdrawing as well as electron donating substituents (Table 2). This method endures various functionalities like nitro, ether, halogens *etc.* on the phenyl ring. Efficacy of this method is fairly general and affords the resultant products in excellent yield (77-91%) and products are obtained by simple work up.



Scheme 4: Proposed mechanism for the synthesis of tertra substituted 1,4-DHPs

In the proposed mechanism (Scheme 4), for the synthesis of tertra substituted dihydropyridine derivatives follow the condensation of **1** and **4** to give **6** by the removal of an acetic acid molecule and at the same time Knoevenagal condensation between **2** and **3** to give **7**, which upon Michal addition with **6** produce **8** then followed by cyclization to produce **9** and rearrange to yield the tetra substituted 1,4-DHP molecule (**5a-5n)**.

2.2 Antibacterial Activity

All the entitled compounds were screened for their antibacterial activity against three Gram-positive bacteria, namely *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus pyogenes* and three gram negative bacteria *Escherichia coli*, *Klebsellia pneumonia*, *Pseudomonas aeruginosa*. The potential of synthesized compounds was compared with a well-known antibiotic drug, Amoxicillin. Minimum inhibitory concentration and zone of inhibition of the screened compounds are depicted in Table 4 and Figure 2. The results of antibacterial analysis reveals that presence of electron releasing groups at the phenyl ring attributed with maximum inhibition against all the tested bacterial strains as compared to electron withdrawing groups attached to the phenyl ring. Interestingly, compounds containing single electron donating group at the *para* position show greater inhibition zone at low MIC value (4 & 8 µg/mL) as compared to the di-substitution (both *meta* and *para*) to the phenyl ring with moderate inhibition zone and high MIC value (8, 16 & 32 µg/mL). Further, it was also observed that phenyl ring substituted with three electron releasing groups (compound **5l**) were completely inefficient against all the bacterial strains. Compound **5b** showed maximum inhibition zone and minimum inhibition concentration of 4 & 8 µg/mL against the all the strains *Staphylococcus aureus* (19 mm), *Bacillus subtilis* (18 mm), *Streptococcus pyogenes* (22 mm), *Escherichia coli* (26 mm), *Klebsellia pneumonia* (21 mm), *Pseudomonas aeruginosa* (26 mm) which is comparable to standard drugs. Further compound **5m** showed potent antibacterial activity against *Staphylococcus aureus* (12 mm), *Bacillus subtilis* (12 mm), *Klebsellia pneumonia* (20 mm) and *Pseudomonas aeruginosa* (18 mm). The compounds **5a & 5c** displayed significant activity against the *Bacillus subtilis* (16 mm), *Streptococcus pyogenes* (17 mm) and *Staphylococcus aureus* (17 mm), *Escherichia coli* (19 mm) at MIC of 8 µg/ml. Compounds **5d** & **5e** exhibited significant activity against *Bacillus subtilis* (15 mm), *Klebsellia pneumonia* (16 mm) and *Staphylococcus aureus* (18 mm), *Streptococcus pyogenes* (18 mm), *Pseudomonas aeruginosa* (19 mm) while compound **5f** displayed activity against the only one strain namely *Escherichia coli* (17 mm). The compound **5j** & **5n** displayed inhibition of bacterial growth against *Staphylococcus aureus* (21 mm), *Streptococcus pyogenes* (17 mm) and *Streptococcus pyogenes* (16 mm), *Escherichia coli* (17 mm) at MIC-8 µg/mL.

Table 4: MIC (µg/mL) of tetra substituted 1,4-DHPs 5a-5n

Entry	Gram (+ve) Bacteria			Gram (-ve) Bacteria		
	S. Aureus	***B. Subtilis***	***S. Pyrogens***	***E. Coli***	***K. Pneumonia***	***P. Aeruginosa***
5a	16 (12)	**8** (16)	**8** (17)	32 (14)	16 (13)	16 (15)
5b	**8** (19)	**8** (18)	**8** (22)	**4** (26)	**8** (21)	**4** (26)
5c	**8** (17)	16 (14)	16 (13)	**8** (19)	16 (13)	16 (13)
5d	16 (13)	**8** (15)	16 (15)	32 (8)	**8** (16)	16 (17)
5e	**8** (18)	16 (17)	**8** (18)	16 (13)	16 (14)	**8** (19)
5f	32 (15)	16 (15)	16 (17)	**8** (17)	16 (12)	16 (16)
5g	16 (17)	32 (11)	16 (14)	16 (15)	32 (10)	32 (11)
5h	16 (16)	32 (12)	16 (12)	32 (10)	32 (9)	16 (13)
5i	32 (12)	16 (14)	32 (10)	16 (16)	32 (9)	16 (14)
5j	**8** (21)	16 (16)	**8** (17)	16 (14)	16 (15)	32 (12)
5k	32 (11)	16 (13)	16 (11)	32 (11)	16 (16)	16 (12)
5l	64 (9)	32 (10)	128 (9)	32 (11)	64 (10)	32 (13)
5m	**8** (12)	**8** (12)	16 (15)	16 (13)	**8** (20)	**8** (18)
5n	16 (10)	16 (15)	**8** (16)	**8** (17)	16 (14)	16 (15)
Amoxicillin	**4 (25)**	**4 (25)**	**4 (25)**	**4 (27)**	**4 (25)**	**4 (25)**

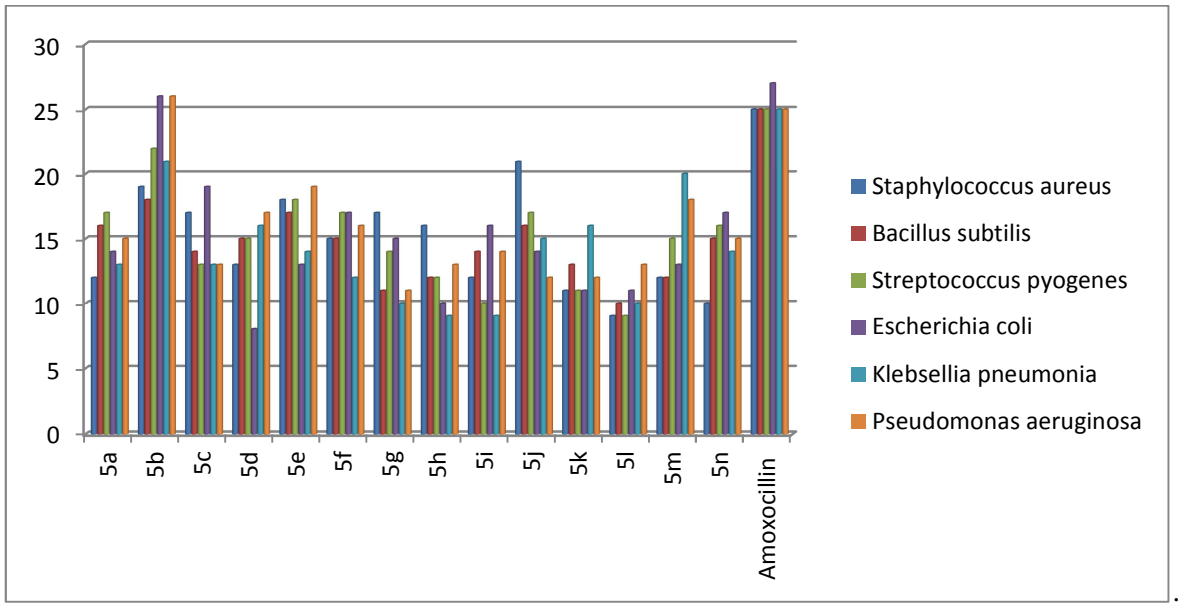


Figure 1: Comparison of diameter of growth of inhibition of the compounds with standard drug

CONCLUSION

$Al(DS)_3$ is an efficient catalyst for production of tetra substituted 1,4-dihydropyridine from readily available starting materials in a single step with inherent flexibility and diversity. This method was efficacious to reduce labor, cost, waste production and also devoid of harsh reaction conditions. The target compounds were obtained in an acceptable yield with simple recrystalization at the purification step. The results obtained from antibacterial studies serve the purpose of our research. Compound **4b** was found to be most active against all the tested strains.

Some structural modifications in these compounds may further lead to the developments of newer and effective antibacterial agents in the future.

Acknowledgements
Authors Harvinder Singh Sohal, Anu Radha and Priyanka Parmar thanks to Chandigarh University, Ghauran Punjab, India for the financial support. Author Manvinder Kaur thanks to Punjabi university for providing basic facilities for research and also grateful to UGC New Delhi for providing MANF-SRF for financial assistance.

REFERENCES

[1] A. Domling, I. Ugi, *Angew. Chem. Int. Ed.*, **2000**, 39, 3168.
[2] L. Weber, *Curr. Med. Chem.*, **2002**, 9, 1241.
[3] A. Hantzsch, *Jusfus Liebigs Ann. Chem.*, **1882**, 215, 1.
[4] R. F. Hutton, F. H. Westheimer, *Tetrahedron*, **1958**, 3, 73.
[5] R. Boer, V. Gekeler, *Drugs of Future*, **1995**, 20, 499.
[6] V. M. Briukhanov, V. I. Zverev-laf Elkin, *Exp. Clin. Pharmacol*, **1994**, 57, 47.
[7] J. M. Tusell, S. J. Serratosa, *Brain Res*., **1993,** 622, 99.
[8] G. A. Wachter, M. C. Davis, A. R. Martin, S. G. Franzblau, *J. Med. Chem.*, **1998**, 41, 2436.
[9] B. Desai, D. Sureja, Y. Naliapara, A. Shah, A. K. Saxena, *Bioorg. Med. Chem.*, **2001,** 9, 1993.
[10] C. E. Sunkel, M. F. de Casa-Juana, L. Santos, M. M. Gomez, M. Villarroya, M. A. Gonzalez-Morales, J. G. Priego, M. P. Ortega, *J. Med. Chem.*, **1990**, 33, 3205.
[11] C. J. Li, T. H. Chan, *Organic Reaction in Aqueous Media*, Wiley: New York, **1997**.
[12] T. F. Moghadam, S. Azizian, *J. Phys. Chem. B*, **2014**, 118, 1527.
[13] (a) J. M. Khurana, S. Kumar, *Tetrahedron Lett.*, **2009**, 50, 4125; (b) A. Khalafi-Nezhad, M. N. Soltani Rad, G. H. Hakimelahi, B. Mokhtari, *Tetrahedron*, **2002**, 58, 10341; (c) M. Sonegawa, M. Yokota, H. Tomiyana, T. Tomiyama, *Chem. Pharm. Bull.*, **2006**, 54, 706; (d) E. Meyer, A. C. Joussef, L. B. P. de Souza, *Synth. Commun.*, **2006**, 36, 729; (e) C. Wang, T. Hang, H. Zhang, *Synth. Commun.*, **2003**, 33, 451.
[14] (a) P. Albonico, I. Blute, E. Borgarello, W. O. Parker Jr, *Coll. Surf.*, **1990**, 48, 13; (b) B. Movassagh, S. Alapour, *Hetroatom. Chem.*, **2013**, 24, 174; (c) M. Esmaeilpour, A. Z. Sardarian, *Iran. J. Sci. Tech.*, **2013**, 37, 277.
[15] R. Thiruvengadathan, Y. Levi-Kalisman, O. Regev, *Ultrasonic Sonochem.*, **2007**, 14, 398.
[16] H. Firouzabadi, N. Iranpoor, A. Khoshnood, *J. Mol. Cat. A: Chem.*, **2007**, 274, 109.
[17] (a) H. S. Sohal, R. Khare, A. Goyal, A. Woolley, K. Singh, R. Sharma, *American J. Chem.*, **2014**, 4, 29; (b) H. S. Sohal, A. Goyal, R. Sharma, R. Khare, S. Kumar, *Eur. J. Chem.*, **2013**, 4, 450.
[18] M. Yusuf, M. Kaur, H. S. Sohal, *J. Het. Chem.*, **2015**, DOI 10.1002/jhet.2530