American Journal of Chemistry 2014, 4(1): 29-34
DOI: 10.5923/j.chemistry.20140401.04

Multi-component Approach for the Synthesis of Fused Dihydropyridines *via* Unsymmetrical Hantzch Condensation Using Glycerol as Green Solvent

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Abstract Some fused 1,4-dihydropyridine derivatives have been synthesized in one-pot, multi-component condensation of dimedone, aldehyde, malononitrile and ammonium acetate using glycerol, an eco-friendly, readily available green solvent which costs virtually nothing. The targeted molecules are obtained in a yield, which is excellent, to say the least. The synthesized compounds were purified by simple recrystallisation.

Keywords Glycerol, Hantzch Condensation, 1,4-Dihyropyridine, Multi-component, Dimedone

1. Introduction

The chemistry of 1,4-dihydropyridines (1,4-DHPs) began in 1882 with Hantzsch condensation[1]. Since then 1,4-dihydropyridine ring has caught the attention due to its link with the biological system in the form of coenzyme, diphosphopyridine nucleotide (DPNH)[2] and also found as a bio-active material. The 1,4-dihydropyridines are an important class of Ca^{2+} channel blockers and are also known to be effective cardiovascular agents for the treatment of hypertension. Apart from these activities, 1,4-DHPs are found to be as PAF-acether antagonists[3], calcium antagonists[4], antihypertensives[5], cerebral antischemic activity in the treatment of Alzheimer's disease and chemosensitizer acting in tumor therapy. Presently, number of 1,4-dihydropyridine based drugs have been commercialised such as nifedipine, felodipine[6], nicardipine[7], amlodipine[8] and many more have appeared in the market[9]. On the other hand, green solvents and solvent from renewable resources has gained much interest in the recent years[10]. Use of water has attracted much attention[11] but water based processes are still subject to limitations due to solubility problems of highly hydrophobic substrates. However, excellent solvent properties like low toxicity [LD_{50} (oral rat) 12600 mg/kg], biodegradability, low-flammability, long liquid range (boiling point 290℃), low vapour pressure and solubility of polar organic compounds has made the glycerol an excellent option to use as solvent for organic synthesis. Further with the present emphasis and increasing demand of biodiesel, which is responsible for the excess production of glycerol as by-product, triggered the discovery of processes that use glycerol for the synthesis of value added chemicals, as reaction medium and for other applications[12, 13]. Recently glycerol has been used for Heck and Suzuki coupling[14], Michael addition[15], Fridel-Crafts type addition, epoxide ring opening[16], synthesis of xanthenes[17] and very recently for the production of benzodiazepines and octahydroacridines[18] *etc*. Understanding the importance of 1,4-DHPs, plethora of reports on the synthesis of 1,4-DHPs and modifications of the original Hantzch reaction appeared in the literature[19-26]. But some of the reported protocols have one or another drawback like collection and purification of catalyst that may cause harmful effects, harsh reaction conditions, unsatisfactory yields, use of harmful solvents, *etc.* Persisting with our work on heterocyclics[27], it is high time when we develop a procedure, which is pro-environment, clean and economical. In the present report, glycerol mediated unsymmetrical hantzch reaction have been reported **(Scheme 1)**.

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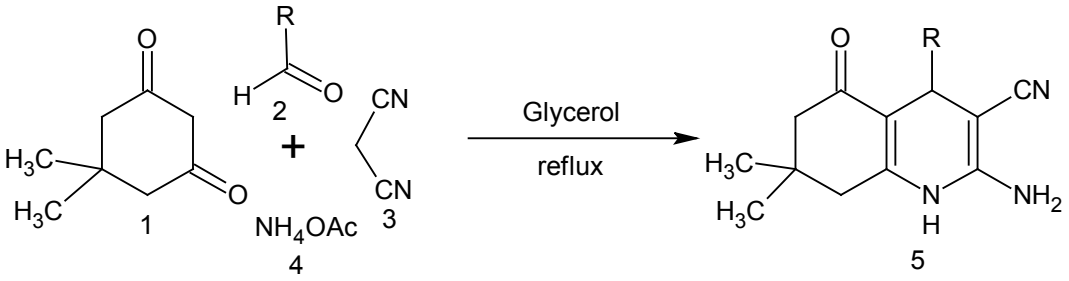
Published online at http://journal.sapub.org/chemistry



Scheme 1.

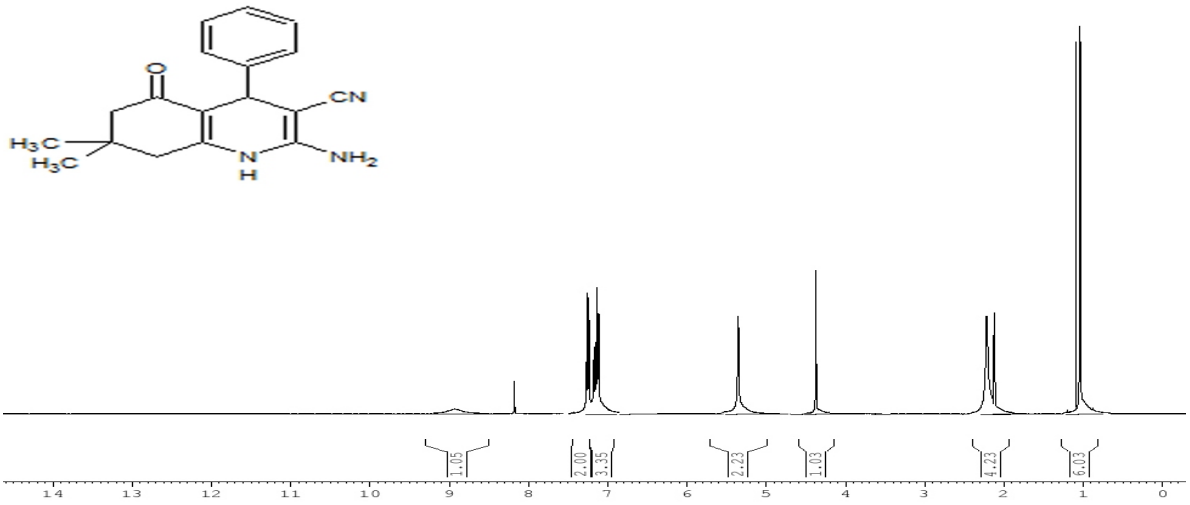


Figure 1. [1]H NMR of the 2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline **5a**

2. Result and Discussion

Table 1. Effect of solvent on the percentage yield of 2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline **5a**

Solvent	Yield[a] (%)
Methanol	87
Ethanol	90
Glycerol	92
Toluene	60
Chloroform	67
Acetonitrile	80

[a]Yield refer to combined amounts of different crops

Table 2. Effect of temperature on the synthesis of 2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline **5a**

S.No.	Temperature (°C)	Yield[a] (%)	Time (hr.)
1	80	48	3
2	90	67	3
3	100	81	2
4	110	92	1
5	120	91	1
6	130	89	1

[a]Yield refer to combined amounts of different crops

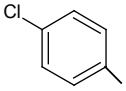
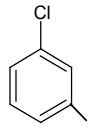
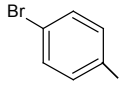
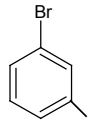
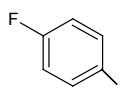
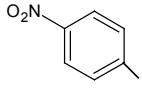
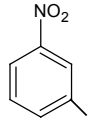
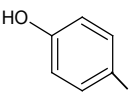
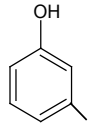
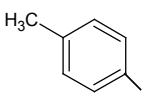
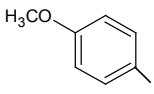
Condensation of dimedone **1**, benzaldehyde **2a**, malononitrile **3** and ammonium acetate **4** were carried out in different solvents like methanol, ethanol, acetonitrile, glycerol, toluene and chloroform. Glycerol as solvent provides the good results as compare to other organic solvents (**Table 1**).

Using glycerol, reaction was carried out at different temperatures and it was found that 110 °C is the optimal temperature. Decreasing temperature, affects the time and yield to a large extent but further rise in temperature will not affect the yield and reaction time as summarized in table 2.

The structure of the compound **5a** was confirmed by the spectral techniques. In IR spectrum absorption at 3436 cm^{-1} represents the N-H stretching, a strong absorption for C=O and C≡N observed at 1719 and 2197 cm^{-1}, while absorption at 3324 and 3214 cm^{-1} represents NH_2 and the aromatic C-H stretching respectively. In ^{1}H NMR spectra peaks for five aromatic protons are observed at δ 7.07-7.29, peak at δ 5.36 for $–NH_2$ protons, peak at δ 4.38for –CH proton, peak at δ 8.94 for –NH proton and two singlet for CH_3 observed at δ 1.02 and δ 1.09. Spectral data of **5a** fully supports the structure assigned to it (Figure 1). Similarly, other 2-Amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline **5 b-l** have been synthesised by the condensation of dimedone **1**, aldehyde **2 b-l**, ammonium acetate **4** and malononitrile **3** in glycerol. The results are summarise in **Table 3**. Reactions proceed smoothly with aldehydes, carrying electron withdrawing as well as electron donating substituents (**Table 3**). This method endures various functionalities like nitro, ether, halogen *etc*. on the aldehydes. Efficacy of this method is fairly general and

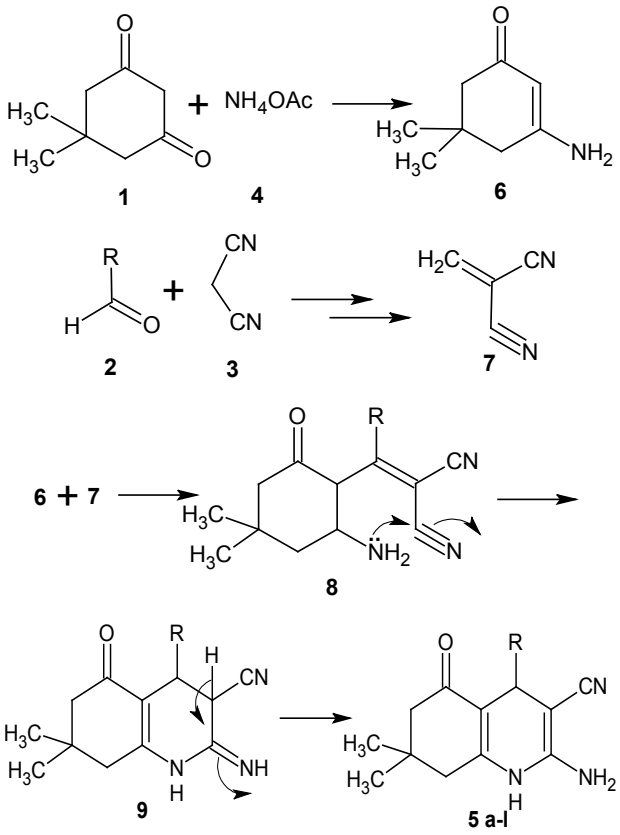
afforded the resultant products in excellent yield (87-92%) and products are obtained by simple work up.

Table 3. Synthesis of fused 1,4-dihydropyridine derivatives

Aldehyde (R)	Product	Yield[a] (%)	Melting point (°C)
	5a	92	277–278
	5b	90	285-287
	5c	91	265-267
	5d	90	283-284
	5e	90	292-294
	5f	91	272-273
	5g	91	284-286
	5h	92	275-276
	5i	89	270-271
	5j	90	283-285
	5k	89	292-294
	5l	87	290-291

[a]Yield refer to combined amounts of different crops

In the proposed mechanism, condensation of **1** and **4** to give **6** followed by the removal of an acetic acid molecule. On the other side Knoevenagal condensation between **2** and **3** produce **7**, which upon Michal addition with **6** produce **8** which undergoes cyclization to generate **9** and **9** rearrange to yield dihydropyridines **5 a-l**.



3. Conclusions

The present procedure is an effective method for production of highly functionalized 1,4-dihydropyridine from readily available starting materials in a single step with inherent flexibility and diversity. Another advantage of this method is minimization of time, labor, cost, less waste production and devoid of harsh reaction conditions.

4. Experimental

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 spectras were recorded in $CDCl_3$ solution on a Bruker Avance II 400 MHz spectrometer; chemical shifts (delta) are reported in ppm relative to TMS as internal standard. The IR spectras were obtained on a Perkin-Elmer 237B spectrometer.

Synthesis of 2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline **5a**: In a conical flask benzaldehyde (0.01 mol), dimedone (0.01 mol), ethyl

malononitrile (0.01 mol), ammonium acetate (0.02 mol) and glycerol (10 ml) were taken and heated at 120℃ for the stipulated time **table 2**. After the completion of reaction (*vide* TLC), reaction mixture was cooled to room temperature and added 50 ml ice-cold water when solid separated out. Filtered and dried, recrystalised from ethanol to afford compound **5a**, 92% yield, mp 277-278℃ (entry 1, Table 3). Similarly, other aldehydes **3 b-l** were reacted with dimedone, malononitrile and ammonium acetate to afford various 1,4-dihydropyridines derivatives **5 b-l** (Table 3).

Spectral data of some selected compounds:

*2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7, 8-hexahydroquinoline (**5a**):* mp. 277–278 °C; IR (KBr): ῡ = 3436, 3324, 3214, 2197, 1719, 1498 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 1.02 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.01–2.37 (m, 4H, 2×CH_2), 4.38 (s, 1H, CH), 5.36 (s, 2H, NH_2), 7.07–7.29 (m, 5H, ArH), 8.94 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ(ppm)* = 27.4, 29.5, 32.8, 36.9, 39.4, 50.8, 59.7, 113.5, 119.7, 126.2, 127.8, 128.4, 143.9, 155.3, 166.3, 197.7. MS (EI) m/z 294.3 (M+). Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.72; H, 6.48; N, 14.33. Found: C, 73.61; H, 6.58; N, 14.31.

*2-Amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo -1,4,5,6,7,8-hexahydroquinoline(**5b**):* mp. 285-287°C; IR (KBr): ῡ = 3437, 3326, 3218, 2188, 1722, 1505 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 0.97 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.02–2.35 (m, 4H, 2×CH_2), 4.17 (s, 1H, CH), 5.48 (s, 2H, NH_2), 7.08–7.19 (m, 4H, ArH), 8.99 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ(ppm)* = 26.8, 29.9, 32.5, 36.7, 39.8, 51.4, 59.3, 113.5, 120.8, 126.6, 127.7, 128.4, 145.5, 155.6, 166.7, 194.8. MS (EI) m/z 327.45 (M+). Anal. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.96; H, 5.50; N, 12.83. Found:C, 65.87; H, 5.44; N, 12.82.

*2-Amino-4-(3-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo -1,4,5,6,7,8-hexahydroquinoline(**5c**):* mp. 265-267°C; IR (KBr): ῡ = 3429, 3328, 3227, 2197, 1720, 1505 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 1.03 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.97–2.38 (m, 4H, 2×CH_2), 4.34 (s, 1H, CH), 5.39 (s, 2H, NH2), 7.21–7.41 (m, 4H, ArH), 8.96 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 27.4, 29.7, 32.7, 36.6, 39.8, 51.4, 59.5, 113.4, 120.8, 126.9, 127.4, 128.5, 143.6, 155.7, 167.5, 193.8. MS (EI) m/z 327.45 (M+). Anal. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.96; H, 5.50; N, 12.83. Found: C, 65.95; H, 5.48; N, 12.83.

*2-Amino-4-(4-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo -1,4,5,6,7,8-hexahydroquinoline (**5d**):* mp. 283-284°C; IR (KBr): ῡ = 3435, 3336, 3223, 2196, 1721, 1504 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 0.97 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.05–2.35 (m, 4H, 2×CH_2), 4.36 (s, 1H, CH), 5.46 (s, 2H, NH_2), 7.02–7.27 (m, 4H, ArH), 8.83 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ(ppm)* = 27.4, 29.6, 32.7, 36.5, 39.5, 50.9, 59.7, 112.9, 119.7, 126.5, 127.5, 128.7, 144.5, 155.6, 169.0, 192.6. MS (EI) m/z 371.9 (M+). Anal. Calcd for $C_{18}H_{18}BrN_3O$: C, 58.08; H, 4.84; N, 11.29. Found: C, 58.02; H, 4.80; N, 11.25.

*2-Amino-4-(3-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo -1,4,5,6,7,8-hexahydroquinoline (**5e**):* mp. 292-294°C; IR (KBr): ῡ = 3428, 3326, 3216, 2197, 1722, 1513 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 0.94 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 2.14–2.47 (m, 4H, 2×CH_2), 4.36 (s, 1H, CH), 5.37 (s, 2H, NH_2), 7.09–7.21 (m, 4H, ArH), 8.90 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ(ppm)* = 27.6, 29.3, 32.6, 36.7, 39.4, 50.9, 59.6, 113.5, 120.6, 126.3, 127.4, 128.7, 144.3, 155.5, 166.8, 196.9. MS (EI) m/z 371.9 (M+). Anal. Calcd for $C_{18}H_{18}BrN_3O$: C, 58.08; H, 4.84; N, 11.28. Found: C, 58.03; H, 4.81; N, 11.31.

*2-Amino-4-(4-fluorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**5f**):* mp. 272-273°C; IR (KBr): ῡ = 3441, 3334, 3213, 2184, 1721, 1503 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 1.01 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.11–2.49 (m, 4H, 2×CH_2), 4.22 (s, 1H, CH), 5.52 (s, 2H, NH_2), 7.16–7.32 (m, 4H, ArH), 8.84 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ(ppm)* = 27.4, 30.1, 32.4, 36.5, 39.7, 50.8, 59.8, 113.5, 121.6, 127.4, 127.5, 128.3, 144.5, 155.7, 167.9, 196.3 ppm; MS (EI) m/z 312.35 (M+). Anal. Calcd for $C_{18}H_{18}FN_3O$: C, 69.44; H, 5.83; N, 13.50. Found: C, 69.40; H, 5.83; N, 13.49.

*2-Amino-4-(4-nitrophenyl)-3-cyano-7,7- dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**5g**):* mp. 284-286°C; IR (KBr): ῡ = 3434, 3325, 3219, 2209, 1725, 1504 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 1.07 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.07–2.49 (m, 4H, 2×CH_2), 4.28 (s, 1H, CH), 5.53 (s, 2H, NH_2), 7.22–7.37 (m, 4H, ArH), 8.90 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ(ppm)* = 26.9, 29.9, 33.0, 37.2, 39.7, 51.5, 59.7, 113.7, 121.1, 127.2, 127.2, 128.5, 144.6, 154.5, 167.6, 195.8. MS (EI) m/z 338 (M+). Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.90; H, 5.32; N, 16.56. Found: C, 63.77; H, 5.32; N, 16.48.

*2-Amino-4-(3-nitrophenyl)-3-cyano-7,7-dimethyl-5-oxo-1 ,4,5,6,7,8-hexahydroquinoline (**5h**):* mp. 275-276°C; IR (KBr): 3423, 3325, 3216, 2196, 1722, 1507 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 1.07 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.20–2.56 (m, 4H, 2×CH_2), 4.59 (s, 1H, CH), 4.77 (s, 2H, NH_2), 7.48–7.75 (m, 4H, ArH), 8.92 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ(ppm)* = 27.3, 30.4, 32.8, 36.9, 39.9, 51.1, 59.6, 112.8, 120.6, 126.8, 127.1, 128.5, 144.6, 155.2, 168.2, 195.4. MS (EI) m/z 338 (M+). Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.90; H, 5.32; N, 16.56. Found: C, 63.81; H, 5.30; N, 16.51.

*2-Amino-4-(4-hydroxyphenyl)-3-cyano-7,7- dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline(**5i**):* mp. 270-271°C; IR (KBr): ῡ = 3436, 3384, 3326, 3204, 2196, 1719, 1497 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 1.05 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.11–2.45 (m, 4H, 2×CH_2), 4.36 (s, 1H, CH), 5.89 (s, 2H, NH_2), 7.07–7.29 (m, 4H, ArH), 8.78 (s, 1H, NH), 9.76 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 26.8, 29.7, 32.7, 36.8, 39.7, 50.6, 59.9, 113.4, 120.8, 126.5, 127.6, 128.2, 144.3, 154.7, 166.7, 194.9. MS (EI) m/z 309 (M+). Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.90; H, 6.15; N, 13.59. Found: C, 69.83; H, 6.13; N, 13.58.

*2-Amino-4-(3-hydroxyphenyl)-3-cyano-7,7- dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline(**5j**):* mp. 283-285°C; IR (KBr): ῡ = 3429, 3383, 3337, 3224, 2202, 1717, 1504 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 0.95 (s, 3H, CH_3),

0.99 (s, 3H, CH_3), 1.99–2.30 (m, 4H, 2×CH_2), 4.29 (s, 1H, CH), 5.47 (s, 2H, NH_2), 7.18–7.29 (m, 4H, ArH), 8.88 (s, 1H, NH), 9.81 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ(ppm)* = 26.9, 29.8, 32.5, 36.6, 39.6, 50.7, 59.6, 113.5, 121.4, 126.6, 127.7, 128.5, 143.8, 158.0, 166.4, 195.8. MS (EI) m/z 309 (M+). Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.90; H, 6.15; N, 13.59. Found: C, 69.77; H, 6.14; N, 13.55.

*2-Amino-4-(4-methylphenyl)-3-cyano-7,7- dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline(**5k**):* mp. 292-294°C; IR (KBr,): 3437, 3320, 3222, 2213, 1718, 1495 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 0.97 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 1.99–2.36 (m, 4H, 2×CH_2), 4.47 (s, 1H, CH), 5.45 (s, 2H, NH_2), 7.02–7.19 (m, 4H, ArH), 8.79 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ(ppm)* = 27.2, 30.3, 32.9, 36.2, 39.2, 50.8, 59.9, 113.5, 121.7, 126.3, 127.6, 128.7, 144.5, 156.7, 168.6, 195.9. MS (EI) m/z 307 (M+). Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.27; H, 6.84; N, 13.68. Found: C, 74.19; H, 6.81; N, 13.62.

*2-Amino-4-(4-methoxylphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline(**5l**):* mp. 290-291°C; IR (KBr): ῡ = 3446, 3329, 3223, 2209, 1717, 1499 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ(ppm)* = 0.95 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 2.10–2.48 (m, 4H, 2×CH_2), 4.28 (s, 1H, CH), 5.57 (s, 2H, NH_2), 7.17–7.39 (m, 4H, ArH), 8.84 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): *δ(ppm)* = 26.7, 29.5, 32.7, 37.4, 39.5, 51.3, 59.2, 114.3, 120.8, 126.9, 127.4, 128.7, 144.5, 156.8, 168.3, 195.8. MS (EI) m/z 323 (M+). Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.58; H, 6.50; N, 13.00. Found: C, 70.45; H, 6.41; N, 13.01.

ACKNOWLEDGEMENTS

The authors thank M. M. University, Mullana, Ambala, India for the financial support and Harvinder Singh Sohal and Arun Goyal also thank Mr. Vikas Pahwa for the liberal support.

REFERENCES

[1] Hantzsch, A., 1882, Ueber die Synthese Pyridinartiger Verbindungen aus. Acetessigather und Aldehydammoniak, Jusfus Liebigs Ann. Chem., 215(1), 1-82.

[2] Hutton, R. F., Westheimer, F. H., 1958, N-methyl dihydronicotinamide, Tetrahedron, 3(1), 73-74.

[3] Sunkel, C. E., de Casa-Juana, M. F., Santos, L., Gomez, M. M., Villarroya, M., Gonzalez-Morales, M. A., Priego, J. G., Ortega, M. P., 1990, 4-Alkyl-1,4-dihydropyridine derivatives as specific PAF-acether antagonists, J. Med. Chem. 33(12), 3205-3210.

[4] Rovnyak, G. C., Kimball, S. D., Beyer, B., Cucinotta, G., DiMarco, J. D., Gougoutas, J., Hedberg, A., Malley, M., McCarthy, J. P., Zhang, R., Moreland, S., 1995, Calcium Entry Blockers and Activators: Conformational and Structural Determinants of Dihydropyrimidine Calcium Channel Modulators, J. Med. Chem., 38(1), 119-129.

[5] Archibald, J. L., Bradley, G., Opalko, A., Ward, T. J., White, J. C., Ennis, C., Shapperson, N. B. 1990, Design of an antithrombotic-antihypertensive agent (Wy 27569). Synthesis and evaluation of a series of 2-heteroaryl substituted dihydropyridines, J. Med. Chem., 33(2), 646-652.

[6] Boström, S. L., Ljung, B., Mårdh, S., Forsen, S., Thulin, E., 1981, Interaction of the antihypertensive drug felodipine with calmodulin, Nature, 292(1), 777-778.

[7] Iwanami, M., Shibanuma, T., Fujimoto, M., Kawai, R., Tamazawa, K., Takenaka, T., Takahashi, K., Murakami, M., 1979, Synthesis of new water-soluble dihydropyridine vasodilators, Chem. Pharm. Bull. 27(6), 1426-1440.

[8] Arrowsmith, J. E., Campbell, S. F., Cross, P. E., Stubbs, J. K., Burges, R. A., Gardiner, D. G., Blackburn, K. J., 1986, Long-acting dihydropyridine calcium antagonists. 1. 2-Alkoxymethyl derivatives incorporating basic substituents, J. Med. Chem., 29(9), 1696-1702.

[9] Goldmann, S., Stoltefuss, J., 1991, 1,4-Dihydropyridines: Effects of Chirality and Conformation on the Calcium Antagonist and Calcium Agonist Activities, Angew. Chem. Int. Ed. Engl., 30(12), 1559-1578.

[10] (a) Handy, S. T., 2003, Greener solvents: room temperature ionic liquids from biorenewable sources" Eur. J. Chem., 9(13), 2938-2944; (b) Leitner, W., 2007, Green Solvents for Processes, Green Chem., 9(1), 923-923; (c) Horváth, I. T., 2008, Solvent from nature" Green Chem., 10(1), 1024-1028; (d) Giovanni, I., Silke, H., Dieter, L., Burkhard, K., 2006, Low melting sugar-urea-salt mixtures as solvents for organic reactions-estimation of polarity and use in catalysis, Green Chem., 8(1), 1051-1055; (e) Clark, J. H., Green chemistry: challenges and opportunities, Green Chem., 1(1), 1-8.

[11] (a) Simon, M. O., Li, C., 2012, Green chemistry oriented organic synthesis in water, J. Chem. Soc. Rev., 41(4), 1415-1427; (b) Butler, R. N., Coyne, A. G., 2010, Water: Nature's Reaction Enforcer-Comparative Effects for Organic Synthesis "In-Water" and "On-Water, Chem. Rev., 110(10), 6302-6337; (c) Chanda, A., Fokin, V. V., Organic synthesis 'on water', 2009, Chem. Rev., 109(2), 725-748; (d) Li, C. J., 2007, Reactions of C−H Bonds in Water, Chem. Rev., 107(6), 2546-2562; (e) Li, C. J., 2005, Organic Reactions in Aqueous Media with a Focus on Carbon−Carbon Bond Formations: A Decade Update, Chem. Rev., 105(8), 3095-3166; (f) Li, C. J., 1993, Organic reactions in aqueous media - with a focus on carbon-carbon bond formation, Chem. Rev., 93(6), 2023-2035.

[12] (a) Pagliaro, M., Ciriminna, R., Kimura, H., Rossi, M., Pina, C. D., 2007, From glycerol to value-added products, Angew. Chem. Int. Ed., 46(24), 4434-4440; (b) Corma, A., Iborra S., Velty, A., 2007, Chemical Routes for the Transformation of Biomass into Chemicals, Chem. Rev., 107(6), 2411-2502; (c) Armaroli, N., Balzani, V., 2007, The Future of Energy Supply: Challenges and Opportunities, Angew. Chem. Int. Ed., 46(1), 52-66; (d) Jerome, F., Pouilloux, Y., Barrault, J., 2008, Rational design of solid catalysts for the selective use of glycerol as a natural organic building block, ChemSusChem., 1(7), 586-613.

[13] (a) Zhou, C. H., Beltramini, J. N., Fan, Y. X., Lu, G. Q., 2008, Chemoselective of Glycerol as a Biorenewable Source to Valuable Commodity Chemicals, Chem. Soc. Rev., 37(3), 527-549; (b) Behr, A., Eilting, J., Irawadi, K., Leschinski, J., Lindner, F., 2008, Improved utilisation of renewable resources: New important derivatives of glycerol, Green

Chem., 10(1), 13-30; (c) Bachhav, H. M., Bhagat, S. B., Telvekar, V. N., 2011, Efficient protocol for the synthesis of quinoxaline, benzoxazole and benzimidazole derivatives using glycerol as green solvent, Tetrahedron Lett., 52(43), 5697-5701.

[14] (a) Wolfson, A., Litvak, G., Dlugy, C., Shotland, Y., Tavor, D., 2009, Employing crude glycerol from biodiesel production as an alternative green reaction medium, Ind. Crops Prod., 30(1), 78-81; (b) Wolfson, A., Dlugy, C., 2007, Palladium- catalyzed Heck and Suzuki coupling in glycerol, Chem. Pap., 61(3), 228-232; (c) Wolfson, A., Dlugy, C., Shotland, Y., 2007, Glycerol as a green solvent for high product yields and selectivities, Environ. Chem. Lett., 5(2), 67-71.

[15] Gu, Y., Barrault, J., Jerome, F., 2008, Glycerol as An Efficient Promoting Medium for Organic Reactions, Adv. Synth. Catal., 350(13), 2007-2012.

[16] Karam, A., Villandier, N., Delample, M., Koerkamp, C. K., Douliez, J. P., Granet, R., Krausz, P., Barrault J., Jerome, F., 2008, Rational Design of Sugar-Based "Surfactant Combined Catalyst" for Promoting Glycerol as Solvent, Eur. J. Chem., 14(33), 10196-10200.

[17] He, F., Li, P., Gu, Y., Li, G., 2009, Glycerol as a promoting medium for electrophilic activation of aldehydes: catalyst-fre e synthesis of di(indolyl)methanes, xanthene-1,8(2H)-diones and 1-oxo-hexahydroxanthenes, Green Chem., 11(1), 1767-1773.

[18] (a) Radatz, C. S., Silva, R. B., Perin, G., Lenardão, E. J., Jacob, R. G., Alves, D., 2011, Catalyst-free synthesis of benzodiazepines and benzimidazoles using glycerol as recyclable solvent, Tetrahedron Lett., 52(32), 4132-4136; (b) Nascimento, J. E. R., Barcellos, A. M., Sachini, M., Perin, G., Lenardão, E. J., Alves, D., Jacob, R. G., Missau, F., 2011, Catalyst-free synthesis of octahydroacridines using glycerol as recyclable solvent, Tetrahedron Lett., 52(20), 2571-2574.

[19] Quiroga, J., Portillo, S., Pérez, A., Gálvez, J., Abonia, R., Insuasty, B., 2006, An efficient synthesis of pyrazolo [3,4-*b*] pyridine-4-spiroindolinones by a three-component reaction of 5-aminopyrazoles, isatin, and cyclic β-diketones, Tetrahedron Lett., 52(21), 2664-2666.

[20] Balamurugan K., Perumal, S., Menéndez, J. C., 2011, New four-component reactions in water: a convergent approach to the metal-free synthesis of spiro[indoline /acenaphthylene-3, 4′-pyrazolo[3,4-*b*]pyridine derivatives, Tetrahedron, 67(18), 3201-3208.

[21] Maheswara, M., Siddaiah, V., Damu, G. L., Venkata Rao, C., 2006, An efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation using heterogeneous catalyst under solvent-free conditions, Arkivoc, 2006(2), 201-206.

[22] Das, B., Ravikanth, B., Ramu, R., VittalRao, B., 2006, An Efficient One-Pot Synthesis of Polyhydroquinolines at Room Temperature Using HY-Zeolite, Chem. Pharma. Bull. 54(7), 1044-1045.

[23] Heravi, M. M., Bakhtiri, K., Javadi, N. M., Bamoharram, F. F., Saeedi, M., Oskooi, H. A., 2007, $K_7[PW_{11}CoO_{40}]$-catalyzed one-pot synthesis of polyhydroquinoline derivatives via the Hantzsch three component condensation, J. Mol. Cat. A: Chem., 264(1), 50-52.

[24] Tajbakhsh, M., Alaee, E., Alinezhad, H., Khanian, M., Jahani, F., Khaksar, S., Rezaee, P., Tajbakhsh, M., 2012, Titanium Dioxide Nanoparticles Catalyzed Synthesis of Hantzsch Esters and Polyhydroquinoline Derivatives, Chinese J. Cat., 33(9), 1517-1522.

[25] Surasani, R., Kalita, D., Rao, A. V. D., Yarbagi, K., Chandrasekhar, K. B., 2012, FeF_3 as a novel catalyst for the synthesis of polyhydroquinoline derivatives via unsymmetrical Hantzsch reaction, J. Fluorine Chem., 135(1), 91-96.

[26] (a) Balalaie, S., Baoosi, L., Tahoori, F., Rominger, F., Bijanzadeh, H. R., 2013, Synthesis of polysubstituted 1,4-dihydropyridines via three-component reaction, Tetrahedron, 69(2), 738-743; (b) Nasr-Esfahani, M., Hoseini, S. J., Montazerozohori, M., Mehrabi, R., Nasrabadi, H., 2014, Magnetic Fe_3O_4 nanoparticles: Efficient and recoverable nanocatalyst for the synthesis of polyhydroquinolines and Hantzsch 1,4-dihydropyridines under solvent-free conditions, J. Mol. Cat. A: Chem., 382(1), 99-105; (c) Kar, P., Mishra, B. G., 2013, Silicotungstic acid nanoparticles dispersed in the micropores of Cr-pillared clay as efficient heterogeneous catalyst for the solvent free synthesis of 1,4-dihydropyridines, Chem. Eng. J., 223(3), 647-656; (d) Reddy, T. R., Reddy, G. R., Reddy, L. S., Meda, C. L. T., Parsa, K. V. L., Kumar, K. S., Lingappa, Y., Pal, M., 2013, Montmorillonite K-10 catalyzed green synthesis of 2,6-unsubstituted dihydropyridines as potential inhibitors of PDE4, Eur. J. Med. Chem., 62(2), 395-404.

[27] (a) Sohal, H. S., Goyal, A., Sharma, R., Khare, R., Kumar, S., 2013, Glycerol mediated, one pot, multicomponent synthesis of dihydropyrano[2,3-c] pyrazoles, Eur. J. Chem., 4(4), 450-453; (b) Sohal, H. S., Goyal, A., Sharma, R., Khare, R., Kumar, S., 2013, Facile and Efficient One-Pot Synthesis of Polyhydroquinoline Derivatives via Unsymmeterical Hantzsch Condensation under Solvent-Free Conditions, Curr. Trends Biotec. Chem. Res., 3(1), 12-16; (c) Kumar, S., Goyal, A., Sohal, H. S., Kumar, S., 2013, A Facile, One Pot, Solvent Free Synthesis of 14-Alkyl or Aryl-14H-dibenzo [a,j]xanthenes and 12-Aryl/alkyl-8,9,10,12-tetrahydrobenzo [a]xanthen-11-one Derivatives, Chem. Sci. Trans., 2(4), 1459-1465.