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A facile synthesis and pharmacological evaluation of 8,8-dimethyl-5-(aryl/heteroaryl)-7,8,9,10-tetrahydro[*b*][1,8]naphthyridine-6(5*H*)-ones as anti-inflammatory and antimicrobial agents

Srinivasa Rao Jetti[1], Anjna Bhatewara[2*], Tanuja Kadre[2] and Shubha Jain[2]

[1]*Department of Chemistry, Narasaraopeta Engineering College, Narasaraopet, Guntur, Andhra Pradesh-522601, India*
[2]*Laboratory of Heterocycles, School of Studies in Chemistry & Biochemistry, Vikram University, Ujjain, Madhya Pradesh-456010, India*

ABSTRACT

8,8-dimethyl-5-(aryl/heteroaryl)-7,8,9,10-tetrahydro[b][1,8]naphthyridine-6(5H)-ones ***5(a-f)*** *were synthesized from 5,5-dimethyl-2-arylidinecyclohexane-1,3-diones* ***3(a-f)*** *on reaction with 2-amino pyrimidine* ***4*** *using Amberlyst 15 DRY as a catalyst in anhydrous ethanol. 5,5-dimethyl-2-arylidinecyclohexane-1,3-diones* ***3(a-f)*** *were synthesized by the reaction of aromatic aldehyde* ***1*** *and dimedone* ***2****, using L- proline as a catalyst in aqueous media. The reactions have the advantages of good yield, easy separation and of being environment friendly. The structures of newly synthesized compounds have been established by spectral, elemental analysis and evaluated for their anti-inflammatory, antibacterial, and antifungal activity.*

Keywords: 1,8-napthyridines, *L*-Proline, Amberlyst 15 DRY, Anti-inflammatory, Antibacterial, Antifungal activity.

INTRODUCTION

Among the nitrogenous heterocycles, naphthyridines and their derivatives represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists due to their exceptionally broad spectrum of biological activities as well as their use as important binding units in the molecular design of synthetic receptors [1]. Naphthyridine derivatives have attracted considerable attention primarily due to the presence of 1,8-naphthyridine skeleton in many compounds which have been isolated from natural substances and exhibit various biological activities [2]. As a heterocyclic moiety, 1,8-naphthyridine also deserves special interest as in its molecule, the arrangement of the nitrogen atoms is optimal for chelation of various metal cations, including lanthanide ions [3].

In parallel to the growing interest in the synthesis of 1,8-naphthyridines to provide biologically active molecules, a large number of publications have reported that several of their derivatives possess antibacterial [4], antimycobacterial [5], antitumor [6], anti-inflammatory [7,8], analgesic [8], antiplatelet [9], gastric antisecretary [10], local anaesthetic [11], anticonvulsant [12] and antihypertensive activity [13,14], besides being associated with β-adrenergic blocking properties [15]. Some 1,8-naphthyridine compounds have been patented as fungicides, bactericides, insecticides, herbicides, anxiolytic, antihypertensives, antiarrhythmics and also as immunostimulants [2,16-19].

Recently, the use of ion exchange resins in organic synthesis has received great attention [20]. Amberlyst 15 DRY [21-22] is a porous sulfonated polystyrene resin that serves as an excellent source of strong acid in nonaqueous media. It has been used in various catalyzed reactions, e.g., esterification, etherification, oxidation, hydration of olefins, condensation, cyclization and electrophilic aromatic substitution. It is easy to measure, safe to use, and readily removed at the end of the reaction. An additional advantage is that the catalyst can be regenerated and used several times. We report here using Amberlyst 15 DRY as catalyst to synthesize 1,8-napthyridine derivatives.

With our continued interest in the synthesis of biologically important heterocyclic systems [23-27] and application of Amberlyst 15 DRY as a heterogeneous catalyst in organic synthesis [28, 29] herein, we wish to report a facile condensation of 5,5-dimethyl-2-arylidinecyclohexane-1,3-diones **3(a-f)** and 2-amino pyrimidine **4** in the presence of catalytic amount of Amberlyst 15 DRY to produce a variety of 8,8-dimethyl-5-(aryl/heteroaryl)-7,8,9,10-tetrahydro[*b*][1,8]naphthy ridine-6(5*H*)-ones **5(a-f)**.

MATERIALS AND METHODS

General

All the chemicals used were of *Sigma-Aldrich* and *E. Merck* make and were used without further purification. Thin layer chromatography was carried out on Merck precoated silica gel 60 F_{254} plates (thickness 0.25 mm). Spots were visualized with UV light at 254 nm for fluorescence quenching spots and at 366 nm for fluorescent spots and with I_2 vapours. When necessary, solvents were distilled and dried according to standard procedures. ^{1}H-NMR and ^{13}C-NMR analyses were carried out on a Bruker AM-400/AV-III 400 spectrometer in $CDCl_3$ and/or DMSO-d_6. Chemical shift values are reported as δ (in ppm) relative to tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on Perkin-Elmer IR spectrophotometer using KBr pellets. Mass spectra were recorded on Joel LCMS spectrophotometer. Anti-inflammatory activity has been carried out in Institute of Pharmacy, Vikram University, Ujjain.

General procedure for the synthesis of 5,5-dimethyl-2-arylidinecyclohexane-1,3-dione 3(a-f)

A mixture of aryl/heteroaryl aldehyde **(1)** (1 mmol), dimedone **(2)** (1.2 mmol) and *L*-proline (3 mol%) in distilled water was stirred for 30 minutes at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (as indicated by TLC) the solid product was separated by filtration and washed with cold water to obtain pure products **3(a-f)** in good yields.

General procedure for the synthesis of 8,8-dimethyl-5-(aryl/heteroaryl)-7,8,9,10-tetrahydro [*b*][1,8] naphthyridine-6(5*H*)-ones 5(a-f)

A mixture of 5,5-dimethyl-2-arylidinecyclohexane-1,3-diones **3(a-f)** (1 mmol), 2-amino pyrimidine **(4)** (1.5 mmol) and Amberlyst 15 DRY (50 mg) in anhydrous ethanol (20 mL) was refluxed for an appropriate time. After completion of the reaction as indicated by TLC, the catalyst was filtered and washed with ethyl acetate until free from organic material. The solvent was evaporated at reduced pressure and obtained solid was recrystallized from ethanol to afford pure napthyridines **5(a-f)** in excellent yields. The physical data (M.p., IR, NMR) of known compounds were found to be identical with those reported in the literature [30]. Spectroscopic data for selected compounds are shown below.

5,5-dimethyl-2-((1-methyl-1*H*-pyrrol-2-yl)methylene-1,3-dione (3a)

M.p. >300; ^{1}H-NMR ($CDCl_3$) δ: 8.38 (-CH=C proton), 6.41-7.70 (pyrrole ring protons), 3.90 (N-CH_3 protons), 2.42 (-CH_2 protons) and 0.98 (-CH_3 protons); ^{13}C-NMR ($CDCl_3$) δ: 190.1, 144.5, 135.6, 129.0, 128.2, 112.8, 107.6, 52.1, 34.8, 31.5, 27.3; IR (ν_{max}.; KBr, cm^{-1}): 3075, 2990, 1715, 1480; LCMS: m/z (%): 231 (M^+), 216, 201.

8,8-dimethyl-5-(1-methyl-1*H*-pyrrol-2-yl)-7,8,9,10-tetrahydro[*b*][1,8]naphthyridine-6(5*H*)-one (5a)

M.p. >300; ^{1}H-NMR ($CDCl_3$) δ: 10.9 (NH proton), 8.10 (pyridine ring proton at C_2), 7.05-7.28 (Ar protons), 5.95-6.10 (pyrrole ring protons), 5.59 (-CH proton), 3.50 (N-CH_3 protons), 2.39 and 1.89 (CH_2 protons), 1.24 and 1.16 (CH_3 protons); ^{13}C-NMR ($CDCl_3$) δ: 195.5, 159.4, 146.0, 138.0, 136.0, 128.2, 125.8, 115.6, 112.5, 110.6, 108.6, 106.0, 43.0, 36.4, 32.4, 29.6, 27.2; IR (ν_{max}.; KBr, cm^{-1}): 3375, 3055, 2970, 1710, 1610, 1480; LCMS: m/z (%): 306 (M^+), 261, 230, 216.

8,8-dimethyl-5-(pyridine-3-yl)-7,8,9,10-tetrahydro[*b*][1,8] naphthyridine-6(5*H*)-one (5b)
M.p. 196-198; ^{1}H-NMR ($CDCl_3$) δ: 11.0 (NH proton), 7.19-8.43 (pyridine ring protons), 4.77 (CH proton), 2.50 and 2.20 (CH_2 protons), 1.18 and 1.05 (CH_3 protons); ^{13}C-NMR ($CDCl_3$) δ: 196.2, 162.8, 149.0, 147.2, 139.7, 136.8, 132.8, 123.0, 114.5, 111.0, 50.5, 40.7, 32.1, 30.0, 29.0, 27.3; IR (ν_{max}.; KBr, cm^{-1}): 3365, 3095, 2965, 1705, 1620, 1515; LCMS: m/z (%): 305 (M^+), 275, 213, 169.

5-(1*H*-indol-3-yl)-8,8-dimethyl-7,8,9,10-tetrahydro[*b*][1,8] naphthyridine-6(5*H*)-one (5c)
M.p. 240-242; ^{1}H-NMR ($CDCl_3$) δ: 10.91 (NH proton), 9.60 (indole ring NH proton), 7.80-7.33 (Ar protons), 5.18 (-CH), 2.61 and 2.15 (CH_2 protons), 1.16 (CH_3 protons); ^{13}C-NMR ($CDCl_3$) δ: 197.9, 158.1, 142.4, 138.1, 136.3, 130.0, 125.0, 124.2, 123.0, 118.9, 113.8, 112.3, 53.1, 43.2, 40.7, 30.2, 28.6; IR (ν_{max}.; KBr, cm^{-1}): 3335, 3095, 2960, 1720, 1625, 1515; LCMS: m/z (%): 343 (M^+), 268, 238, 212, 194.

8,8-dimethyl-5-phenyl-7,8,9,10-tetrahydro[*b*][1,8] naphthyridine-6(5*H*)-one (5d)
M.p. 209-211; ^{1}H-NMR ($CDCl_3$) δ: 11.9 (NH proton), 8.19-7.15 (Ar-protons), 5.50 (CH proton), 2.60 and 2.05 ($2CH_2$ protons), 1.21 and 1.05 (CH_3 protons); ^{13}C-NMR ($CDCl_3$) δ: 190.5, 156.8, 146.0, 138.0, 136.4, 128.2, 126.8, 125.8, 115.6, 111.6, 109.1, 47.0, 46.4, 32.7, 29.6, 27.4; IR (ν_{max}.; KBr, cm^{-1}): 3355, 3075, 2990, 1715, 1615, 1485; LCMS: m/z (%): 304 (M^+), 228.

Pharmacology
Colony bred healthy rats of Wistar strain and albino mice procured from local market of Ujjain were used for the study. They were housed in standard polypropylene cages under room temperature (24 ± 2^0C), relative humidity (60%-70%) and exposed to 12:12 hours light: dark cycle. The rats were fed nutrilab rodent feed and drinking water filtered through an aquaguard water filter system *adlibitum.* They were allowed to acclimatize for 5 days prior to commencement of dosing. Indomethacin was used as a standard drug for comparing the anti-inflammatory effect. The protocol was ethically approved by IAEC of the institute.

Anti-inflamatory activity
The anti-inflammatory activity was determined *in vivo* [31] using the carrageenan-induced rat paw edema test [32, 33]. A solution of 0.1 ml of 1% carrageenan (Sigma-Aldrich, Dorset, UK) in saline was injected sub plantarly in the right hind paw of the rats 1 h after IP administration of compounds. The paw thickness was measured from the ventral to the dorsal surfaces using a dial caliper immediately prior to carrageenan injection and then at each hour, up to 4 h after the sub planar injection. The edema was calculated as the thickness variation between the carrageenan and saline treated paw. Anti-inflammatory activity was expressed as the percent of inhibition of the edema when compared with the control group. The results are expressed as the mean ± SEM of *n* animals per group. The data was statistically analyzed by one way analysis of variance (ANOVA) followed by Tukey multicomparison test. Differences with $P<0.05$ between experimental groups were considered statistically significant.

A ring was marked on the left paw of each animal so that constant length of paw could be dipped each time. The initial paw volume (of left leg) of each rat was measured using plethysmometer. One hour after oral administration of aqueous suspension of Indomethacin and test drug all the rats were challenged by an injection of 0.05 ml of 1% *w/v* solution of carrageenan prepared by dissolving carrageen (1 g) in 0.9% saline into the planter side of the left hind paw. The maximum volume administrated was kept 0.1 mL. The paw volume was measured by using plethysmometer immediately after injection, 1hr, 2hrs, 3hrs, 4hrs, after challenge with carrageenan and the percent increase in the paw volume before and after sub plantar injection of carrageenan was calculated [34].

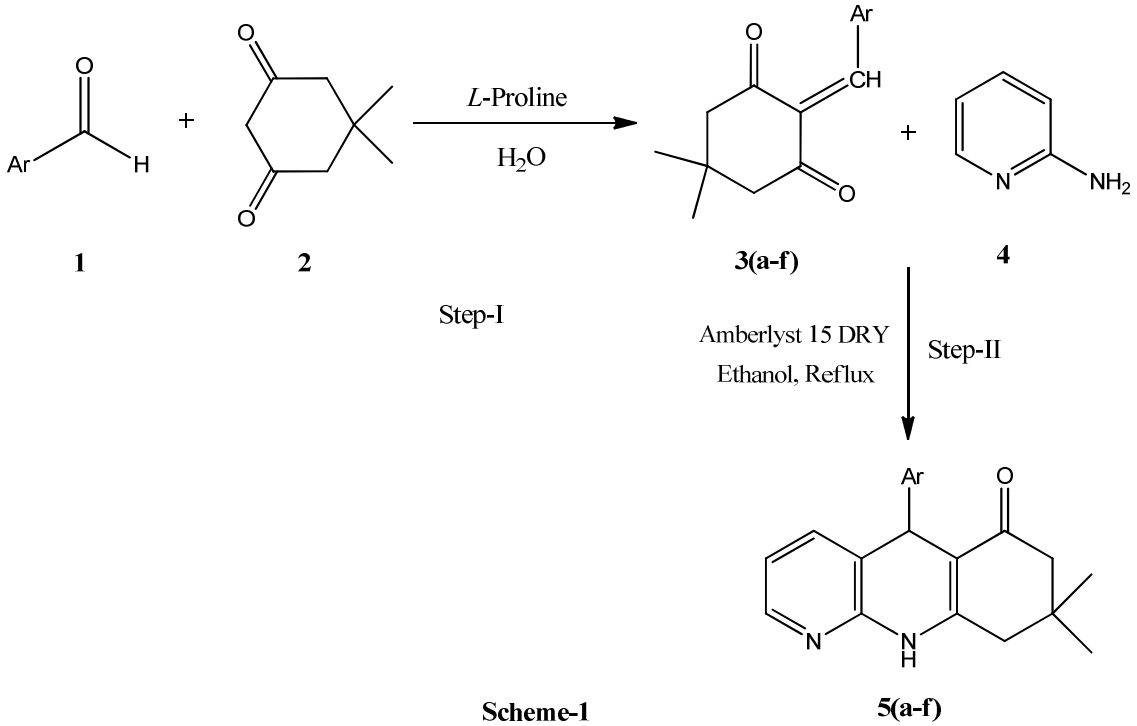
Antibacterial activity
The sensitivity test of the test compounds to the isolated bacteria was done by agar-diffusion technique [35]. Stock solution of a concentration 10 *mg/mL* of each compound was prepared in dimethyl sulphoxide (DMSO). 20 *μL* of each of the solution was adsorbed on sterile 6 *mm* Whattmann filter paper (#4) discs and kept for few hours under vacuum to remove the solvent.

Grown cultures were stored in TSB (Tripticase Soya Broth) oxide maintaining the pH 7.3 in 0.5% agar at 4^0C in the screw capped tubes. Trypticase soya agar (DIFCO) plates were inoculated with standard suspension of different bacterial cultures containing 10^7 *c.f.u/mL* using sterile cotton swabs to obtain a confluent lawn. The prepared discs were placed on the surface at different positions and plates were incubated at 37^0C for 24 hrs. The results were recorded by measuring the zones of inhibition in *mm* against each compound and are reported in Table **6**.

Antifungal activity

The antifungal activity of the synthesized compounds was studied against three fungal cultutres [36]. Saboraud's dextrose-agar was seeded with 10^5 *c.f.u./mL* (colony forming units) fungal spore suspension and transferred to petriplates. 20 μL (10 *mg/mL*) of all compound solutions were impregnated onto the discs of 6 *mm* diameter. The discs were then kept under vacuum for few hours to evaporate solvent. Then the discs were placed at different positions on agar surface. The plates were incubated at 37^0C for 7 days. The results were recorded as zones of inhibition in *mm* and reported in Table **7.**

RESULTS AND DISCUSSION



Aryl/heteroaryl substituted naphthyridines **5(a-f)** were synthesized by the reaction of 2-amino pyrimidine **(4)** with 5,5-dimethyl-2-arylidinecyclohexane-1,3-dione **3(a-f)** (Step **II**, Scheme **1**) the latter were synthesized by Knoevenagel condensation of aryl/heteroaryl aldehydes with dimedone as shown in Step-**I**.

Table 1: Physical data of 5,5-dimethyl-2-arylidinecyclohexane-1,3-diones 3(a-f)

Entry	Ar	Time (min.)	Product[a]	Yield[b] (%)	M.P.(^{0}C)	
					Found	Reported
1	1- CH_3-C_4H_3N	15	**3a**	98	>300	-
2	C_5H_4N	30	**3b**	92	195-197	196-198
3	C_8H_6N	30	**3c**	95	162-164	161-163
4	C_6H_5	30	**3d**	96	265-267	264-266
5	4-OCH_3-C_6H_4	30	**3e**	90	127-129	126-128
6	4-NO_2-C_6H_4	20	**3f**	94	143-145	144-146

[a]*Aryl/heteroaryl aldehyde **(1)** (1 mmol), dimedone **(2)** (1.2 mmol) and L-proline (3 mol%) in distilled water stirred for 30 minutes at room temperature.* [b]*Isolated Yields.*

Table 2: Physical data of 8,8-dimethyl-5-(aryl/heteroaryl)-7,8,9,10-tetrahydro [*b*][1,8]naphthyridine-6(5*H*)-ones 5(a-f)

Product[a]	Ar	Time (Hrs.)	Yield[b] (%)	M.P. (^{0}C)	Elemental Analysis	
					Calculated	Observed
5a	1- CH_3-C_4H_3N	2	93	>300	C, 74.24; H, 6.89; N, 13.67	C, 73.95; H, 6.58; N, 13.08
5b	C_5H_4N	2	85	196-198	C, 74.73; H, 6.27; N, 13.76	C, 74.26; H, 6.11; N, 13.18
5c	C_8H_6N	2.5	90	240-242	C, 76.94; H, 6.16; N, 12.24	C, 76.54; H, 5.83; N, 12.02
5d	C_6H_5	2	91	209-211	C, 78.92; H, 6.62; N, 9.20	C, 78.34; H, 6.12; N, 8.85
5e	4-OCH_3-C_6H_4	2	94	193-195	C, 75.42; H, 6.63; N, 8.38	C, 75.21; H, 6.26; N, 8.16
5f	4-NO_2-C_6H_4	2.5	92	220-222	C, 68.75; H, 5.48; N, 12.03	C, 68.43; H, 5.23; N, 11.79

*[a]5,5-dimethyl-2-arylidinecyclohexane-1,3-diones **3(a-f)** (1 mmol), 2-aminopyrimidine **(4)** (1.5 mmol) and Amberlyst 15 DRY (50 mg) in anhydrous ethanol (20 mL) was refluxed for an appropriate time. [b]Isolated Yields.*

In order to optimize the reaction conditions, the synthesis of compound **5e** was used as a model reaction. A mixture of 2-(4-methoxybenzylidine)-5,5-dimethylcyclohexane-1,3-dione **(3e)** (1 mmol), 2-amino pyrimidine **(4)** (1.5 mmol) and different amounts of Amberlyst 15 DRY was taken (Table **3**). The efficiency of the reaction is affected mainly by the amount of Amberlyst 15 DRY. No products were produced in the absence of the catalyst (entry **1**). Increasing the amount of the catalyst increased the yield of the product. The optimal amount of Amberlyst 15 DRY was 0.05 g (entry **4**), increasing the amount of the catalyst beyond this value did not increase the yield noticeably (entries **5, 6**).

Table 3: Reaction of 2-(4-methoxybenzylidine)-5,5-dimethylcyclohexane-1,3-dione and 2-amino pyrimidine in presence of different amounts of Amberlyst 15 DRY

Entry	Catalyst Loading (g)	Time (h)	Yield[a] (%)
1	Nil	10.0	Nil
2	0.01	8.0	63
3	0.03	5.0	82
4	0.05	2.0	94
5	0.07	2.0	94
6	0.09	3.0	95

Reaction Conditions: 2-(4-methoxybenzylidine)-5,5-dimethylcyclo hexane-1,3-dione (1 mmol) and 2-amino pyrimidine (1.5 mmol) in ethanol under reflux. [a] Isolated yields

Furthermore, to investigate the effect of solvent the same model reaction was carried out in different solvents. As shown in Table **4**, ethanol was found to be the best choice among the solvents screened.

Table 4: Synthesis of naphthyridines using different solvents[a]

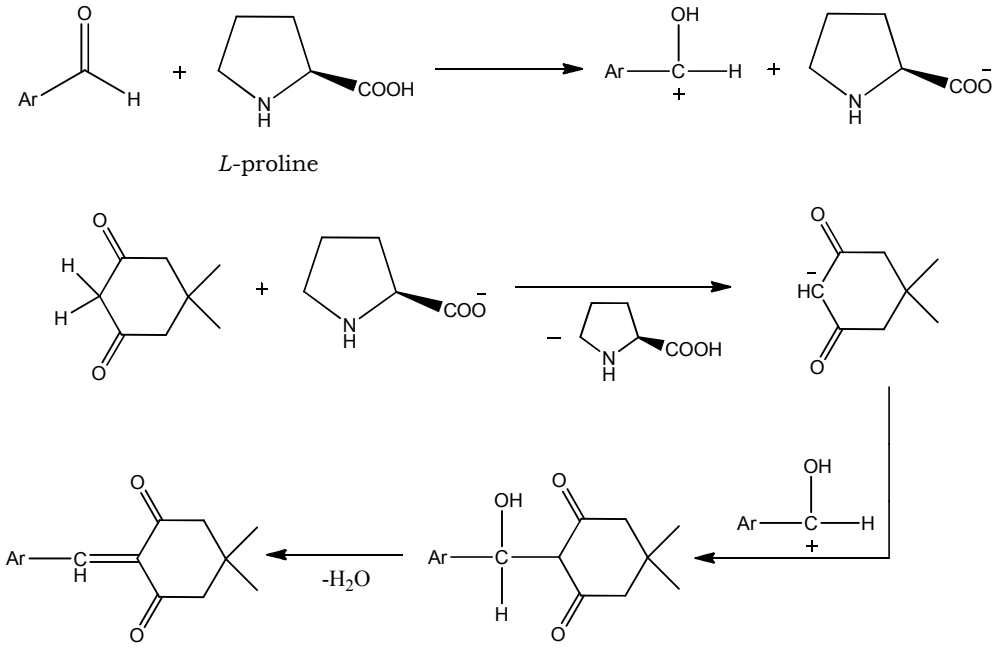
Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	Amberlyst 15 DRY	H_2O	3	85
2	Amberlyst 15 DRY	CH_3OH	4	79
3	Amberlyst 15 DRY	C_2H_5OH	2	94
4	Amberlyst 15 DRY	CH_3CN	3	90
5	Amberlyst 15 DRY	$CHCl_3$	5	71
6	Amberlyst 15 DRY	CH_2Cl_2	6	63

[a]All reactions were carried out at reflux temperature

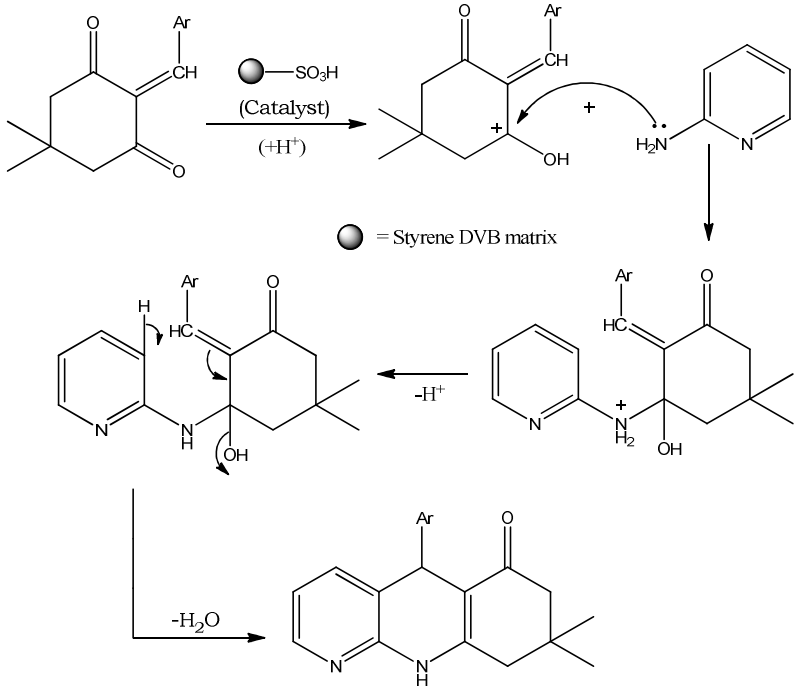
The synthetic route for obtaining the final products is presented in Scheme-**1**. The cyclocondensation of 2-amino pyrimidine with dimedone and substituted aromatic aldehydes yielded 5-(4-substitutedphenyl)-8,8-dimethyl-7,8,9,10-tetrahydro[*b*][1,8]naphthyridine-6(5*H*)-ones. The structures of the compounds **5(a-f)** were assigned on the basis of spectral and analytical data. The reaction was found to be tolerating a range of aryl and heteroaryl groups with different electronic demands including aromatic rings having electron donating and electron withdrawing groups (Table **2**).

In the first step, aryl aldehydes were treated with dimedone in presence of *L*-proline to get 5,5-dimethyl-2-arylidinecyclohexane-1,3-diones **3(a-f)** by Knoevenagel condensation. In the second step, **3(a-f)** were treated with 2-amino pyrimidine in presence of Amberlyst 15 DRY. The 5,5-dimethyl-2-arylidinecyclohexane-1,3-diones undergoes condensation with 2-amino pyrimidine followed by cyclisation with 1,4-elimination of H_2O to form the desired product as per the mechanism proposed (Scheme **2**).

Step-1:



Step-2:



Scheme-2: Plausible mechanismm for the formation of naphthyridine derivative

The reusability of the catalyst was also investigated. For this purpose, the same model reaction to synthesize the compound **5e** was again studied under the optimized conditions. After completion of the reaction, the catalyst was separated by simple filtration due to its heterogeneous nature and washed with ethyl acetate to free from organic material and dried at 100^0C under vacuum for 2 h and reused for the same reaction process. As shown in Fig. **1**, the catalyst could be reused for four times with only slight reduction in its catalytic activity.

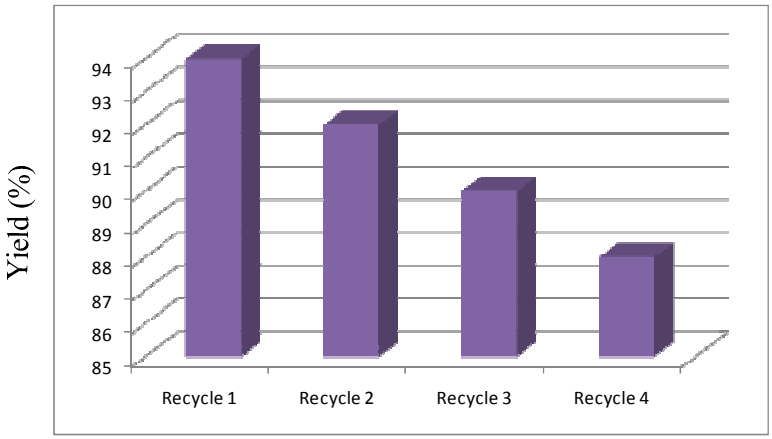


Fig.1: Reusability of Amberlyst 15 DRY for the synthesis of 5e

Anti-inflammatory results of the synthesized compounds **3a, 5(a-d)** with respect to Indomethacin are reported in Table **5**. It is clear from the results that the inhibition percentage is more for compounds **5a** and **5b** showed good anti-inflammatory activity. The inhibition percentage of compounds **5c** and **5d** is low and showed moderate anti-inflammatory activity while the inhibition percentage of compound **3a** is very low and showed poor anti-inflammatory activity.

Table 5: Effects of compounds 3a & 5(a-d) and indomethacin in the inhibition of carrageenan-induced rat paw edema

S. No	Drug	Dose	Paw volume response in milliliters at different time interval in Mean ± SEM			
			1 hour	2 hour	3 hour	4 hour
1	**Control**	10 ml/kg	0.5912± 0.005***	0.5930± 0.002***	0.6102± 0.002***	0.6303± 0.002***
2	**Indomethacin (Standard)**	100 mg/kg	0.2700± 0.005** (54.33%)	0.3124± 0.005** (47.31%)	0.3133± 0.008** (48.65%)	0.3500± 0.005** (44.47%)
3	**3a**	40 mg/kg	0.4035 ± 0.005** (31.78%)	0.4309 ± 0.003** (27.48%)	0.5143± 0.008*** (15.88%)	0.5159± 0.005*** (18.02%)
4	**5a**	20 mg/kg	0.3500 ±0.005** (40.24%)	0.3014 ± 0.005** (49.17%)	0.3243 ± 0.003** (46.85%)	0.3507± 0.005** (44.47%)
5	**5b**	20 mg/kg	0.3900± 0.008** (34.03%)	0.3254 0.003** (45.12%)	0.3015 0.008** (50.58%)	0.3792 0.005** (39.83%)
6	**5c**	20 mg/kg	0.4109± 0.005** (30.49%)	0.4076± 0.005** (31.26%)	0.3876± 0.005** (36.47%)	0.3512± 0.008** (44.28%)
7	**5d**	20 mg/kg	0.3367± 0.005** (40.04%)	0.3950 0.003** (33.38%)	0.4058 0.005** (33.49%)	0.3623 0.003** (42.51%)

Values are expressed as mean ±SEM; n=6 in each group,
****P < 0.001, **P < 0.01, Compared to control.*
Data was analyses by one way ANOVA followed by Duneet's test.

The newly synthesized compounds **5(a-d)** & **3a** were tested against two Gram +ve and two Gram -ve bacteria and the results indicated that the compounds **5b, 5d** and **3a** are highly active against all Gram +ve and Gram -ve bacteria while **5a** and **5c** showed moderate activity (Table **6**). The compound **3a** is highly active against Gram +ve bacteria *Bacillus subtilis* but moderate active against Gram -ve bacteria *Salmonella typhi* and *Escherichia coli*.

Table 6: Antibacterial activity (*in vitro*) of compounds 5(a-d) & 3a (zone of inhibition in *mm*)

Culture	Compound					
	Standard (Ciprofloxacin)	5a	5b	5c	5d	3a
Gram +ve bacteria						
Basillus subtilis	34	26	25	24	22	28
Micrococcus	25	18	22	20	24	20
Gram +ve bacteria						
Salmonella typhi	16	10	20	12	10	10
Escherichia coli	18	14	18	15	12	12
DMSO	-	-	-	-	-	-

The newly synthesized compounds **5(a-d)** & **3a** have also been screened for antifungal activity against three fungi *Aspergillus nigar*, *Aspergillus flavus* and *Alternaria*. Almost all the compounds showed antifungal activity. Among these compounds, **5b** and **5c** showed good antifungal activity against all the fungi but compound **5b** was inactive against *Alternaria*. The remaining compounds **5a, 5d** and **3a** had found to be milder active against all fungi tested.

Table 7: Antifungal activity (*in vitro*) of compounds 5(a-d) & 3a (zone of inhibition in mm)

Culture	Compound					
	Standard (Griseofulvin)	5a	5b	5c	5d	3a
Aspergillus Niger	14	14	20	22	18	10
Aspergillus Flavus	12	10	25	16	10	08
Alternaria	26	22	-	20	20	24
DMSO	-	-	-	-	-	

CONCLUSION

We have synthesized a series of functionalized 8,8-dimethyl-5-(aryl/heteroaryl)-7,8,9,10-tetrahydro[*b*][1,8]naphthyridine-6(5*H*)-ones in good yields by simple and efficient reactions using *L*-proline and Amberlyst-15 DRY as a catalysts respectively. All the proposed reactions allowed the preparation of products without further purification. The newly synthesized 1,8-naphthyridines were well characterized by spectroscopic means and compounds have shown good antiinflammatory, antibacterial, and antifungal activities.

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