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Domino Synthesis of Functionalized 1, 6-Naphthyridines and their *in vitro* Anti-inflammatory and Anti-oxidant Efficacies

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Bioactive 1, 6-naphthyridines were constructed through a one pot multicomponent method by reacting different ketones with malononitrile and pyrrolidine. In vitro anti-inflammatory and 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging activities for all the synthesized 1, 6-naphthyridines were further carried out. These results clearly show that compound **3e** exhibited excellent anti-inflammatory activity with a percentage inhibition of 81.24±4.46 by membrane stabilization method and 77.85±0.46 by the albumin denaturation method at a concentration of 100 µg ml^{-1}, which is comparable to the standard Diclofenac. A noticeable DPPH scavenging activity of 82.08±1.81 % was also observed for the synthesized compounds when compared with the standard, Ascorbic acid.

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Introduction

In recent days, multicomponent reactions (MCRs) have gained considerable scientific interest because of their wide scope of applications in heterocyclic, medicinal and in combinatorial chemistry. The significant features of MCRs involve the production of complex structures with several bonds breaking and making in a one step reaction with high atom economy. Therefore, the chemoselectivity in MCRs is of noticeable significance to develop synthetic strategies for various molecules of target with required chemical modifications.[1] Highly substituted pyridines are considered as supreme class among the different heteroaromatic compounds as they form the basis for many different synthetic organic moieties, pharmaceuticals and natural products. [2,3] These pyridine structures are the most significant because of their wide spectrum of promising biological activities such as anticonvulsants,[4] anti-inflammatory,[5] antimitotic,[6] agents antioxidant,[7,8] anticancer,[9,10] and antimicrobial activities.[11] Similarly, 1,6-naphthyridines[12-17] have established significant attention due to their broad range of bioactivities[18-24] such as antimicrobial,[25] anti-analgesic,[26] antifungal,[27,28] anticancer,[29-31] antioxidant,[31] anti-inflammatory,[27-29,32] antiarrhythmic,[33] antitumor [34], anti HSV-1[35] anti-HIV[36,37] activities and act as inhibitors of acetylcholinesteras.[38] Structures of few previously reported biologically active 1,6-naphyridines (**A-G**) are shown in **Figure 1**.

Numerous synthetic methods have been developed for the synthesis of substituted/fused naphthyridines which include Skraup type reaction,[39] acid catalysed cyclization reaction,[40] multi-component reactions,[41,42] nucleophilic substitution reaction[43] and several other methods.[44-46] Ramakrishnan *et al*., have reported the synthesis of 1, 6-naphthyridines by the reaction of enones with malononitrile and pyrrolidine in ethanol.[47, 48] They have also reported the synthesis of nicotinonitrile and pyridinenitrile derivatives by the reaction of aldehyes with malononitrile in the presence of pyrroldine. [49] In this line, it was of immense interest to explore the reaction of ketones with malononitrile in the presence of pyrrolidine.

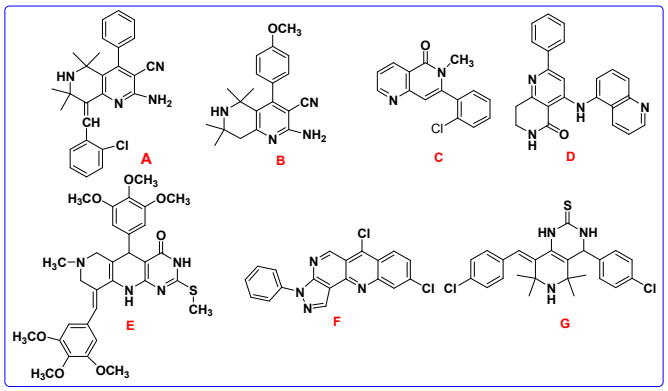

Fig 1. Previously reported bioactive 1,6-naphthyridines

Result and discussions

2.1 Chemistry

In this work, it was intended to synthesize 1, 4-dihydropyridines **2** by reaction of ketones with two equivalents each of pyrrolidine and malononitrile as shown in **Scheme 1**.

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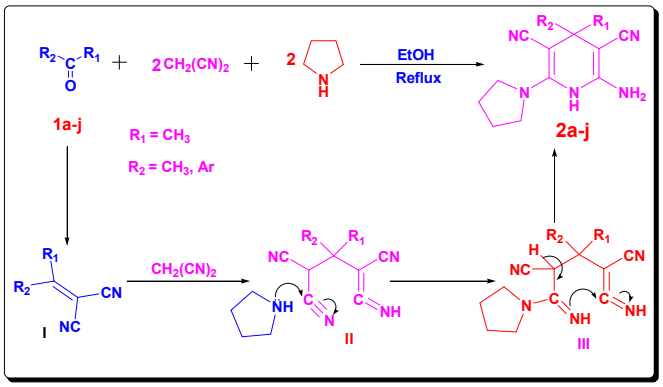
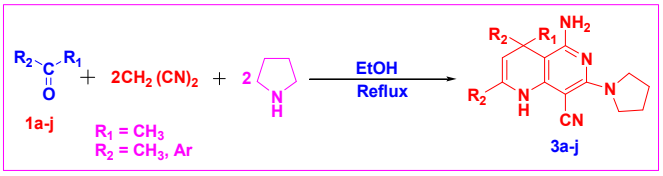


Scheme 1 Planning for the synthesis of 1,4-dihydropyridinedinitriles

Hence, to start with, one equivalent acetophenone was treated with two equivalents each of pyrrolidine and malononitrile under various reaction conditions (**Table 1**). Careful analysis of the spectral data indicated that the product formed is of 1,6-naphthyridine **3**, and not the expected 1,4-dihydropyridines **2 (Scheme 2, Table 2)**.



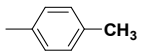
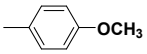
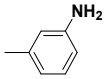
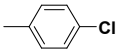
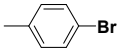
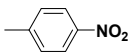
Scheme 2 Synthesis of 1, 6-naphthyridines

In order to optimize the reaction (**Table 1**), various conditions such as grinding, ultra sonication, microwave irradiation and reflux in different solvents were tried. Although the reaction time is less for grinding, ultra sonication and microwave irradiation methods, the conventional reflux in ethanol (**Table 1, entry 7**) was found to be better based on the obtained yield. Hence, various substituted 1,6-napthyridines **3a-j** were prepared under this condition (**Table 2**). Moderately low yield was obtained for electron-withdrawing nitro substituted derivative when compared with other electron-donating substituents and hence the electron density of the substituent may have a role in facilitating the reaction.

Table 1 Reaction condition optimization for the synthesis of 1, 6- naphthyridines **3**.

Entry	Method & Condition	Solvent	Time	Yield (%)
1	Grinding	-	1 h	18
2	Ultra sonication (50 °C)	Ethanol	7 h	20
3	Microwave (210W)	-	7 min.	12
4	Microwave (210W)	Water	45 min.	25
5	Microwave (210W)	Ethanol	45 min.	28
6	Reflux	Toluene	24 h	45
7	Reflux	Ethanol	16 h	73
8	Reflux	Methanol	20 h	56

Table 2 Synthesis of 1, 6-naphthyridines

Entry	Product	R_1	R_2	Yield (%)
1	**3a**	CH_3		71
2	**3b**	CH_3	CH_3	73
3	**3c**	CH_3	CH_2CH_3	70
4	**3d**	CH_3		72
5	**3e**	CH_3		68
6	**3f**	CH_3		74
7	**3g**	CH_3		72
8	**3h**	CH_3		78
9	**3i**	CH_3		60
10	**3j**	CH_3		65

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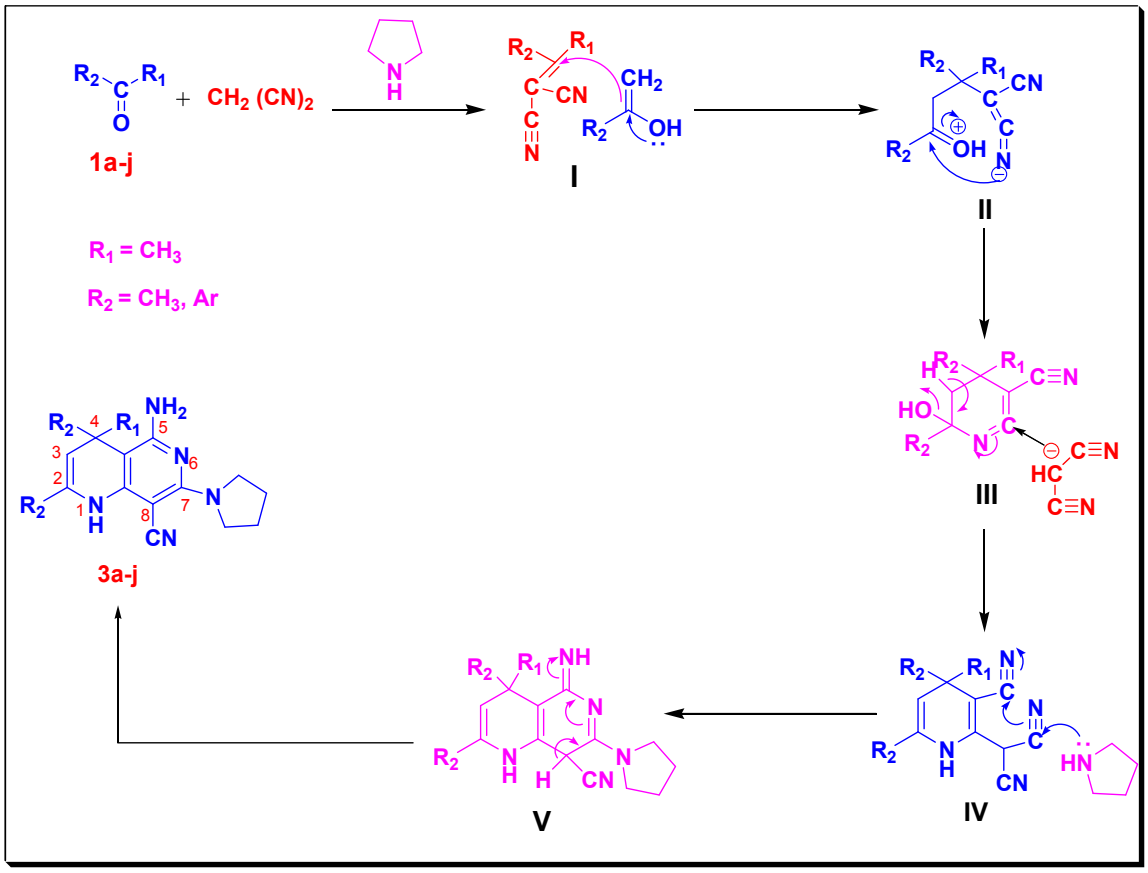


Scheme 3 Mechanistic path way of 1, 6-naphthyridines

The probable mechanism (**Scheme 3**) for the formation of **3** may involve condensation of one molecule of acetophenone with a molecule of malononitrile, in the presence of pyrrolidine as catalyst, to give the intermediate **I** with the elimination of water. Subsequently, Michael type attack by another molecule of acetophenone on the olefinic carbon of the enolic form of the condensed product **II**, followed by nucleophilic attack by cyano nitrogen on the carbonyl carbon lead to a cyclized intermediate **III**, with the elimination of another molecule of water. Another molecule of malononitrile attacks the imino carbon in **IV**, which further attack by a molecule of pyrrolidine (act as reactant) on the cyano carbon lead to the intermediate **V**. This intermediate undergoes amino-imino tautomerization including 1, 5-hydrogen shift to afford the final product, 1, 6-naphthridines (**3a-j**). During the course of the reaction, a molecule of pyrrolidine acted as catalyst and another molecule of the same acted as a reactant.

In the same manner, other ketones were treated with malononitrile in the presence of pyrrolidine. The products obtained **3b-j** was characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. In the case of acetone **3b**, the product obtained was crystallized out as crystalline rods in ethyl acetate, and found suitable for XRD measurement.

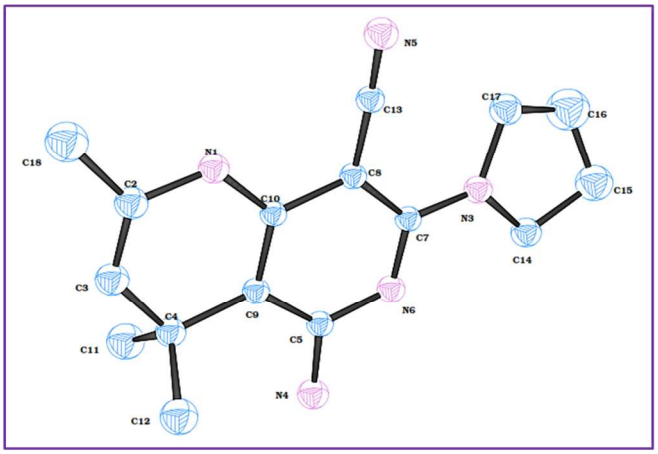
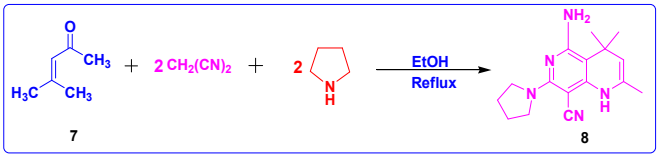


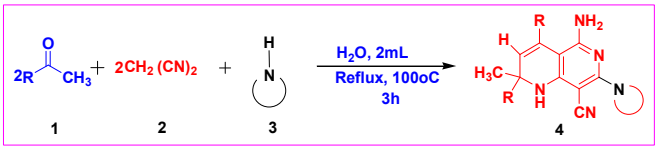
Fig. 2 ORTEP diagram of the compound **3b**, molecular structure showing 30% probability displacement ellipsoids with numbering scheme.

The ORTEP diagram of the derivative **3b** (**Figure 2**) shown to be 1, 6-naphthyridine, which is exactly matching with the reported[49] 1, 6-naphthyridine compounds, prepared by reacting enone of acetone with malononitrile and pyrrolidine **(Scheme 4)**.[50] The other spectroscopic data were also matching with each other. Hence, the formation of 1, 6-naphthyridines was confirmed from the forgoing evidences.



Scheme 4 Synthesis of 5-Amino-1, 4-dihydro-2, 4, 4-trimethyl-7-(pyrrolidin-1-yl)-1, 6-naphthyridine-8-carbonitrile from enones

We also found that the 1, 6-naphthyridines obtained in our reaction condition were regio isomers of the products reported[51] by Chhanda mukhopadhyay *et al*., where two equivalents of ketones reacted with two equivalents of malononitrile and one equivalent of piperidine / morpholine in water medium (**Scheme 5**).



Scheme 5 Synthesis of 1, 6-naphthyridines in water medium

3 Biological evaluations

3.1 *In vitro* anti-inflammatory studies[52, 53]

In vitro anti-inflammatory activities were performed for the prepared 1, 6-naphthyridines and a comparative study with standard drugs was carried out by two different reported methods, such as the albumin denaturation assay and the membrane stabilization method.

A. RBC membrane stabilization method

The key reason for the inflammation involves the blocking of lysosomal release from the neutrophils which is due to the RBC membrane stabilization by anti-inflammatory agents. This method involves the collection of 10 ml of healthy human blood and transferring to centrifugation tubes containing heparin. The blood was then centrifuged (3000 rpm, 5 min.) and further the tubes were washed twice with saline and later reconstituted as 10 % v/v RBC suspensions using normal saline.

Equal quantities of 10 v/v RBC suspension and various concentrations of test samples i.e 50, 75 and 100 µg ml^{-1} were added into different test tubes. Saline solution and Diclofenac were treated as control and standards for the experiment respectively. Further the reaction mixtures were kept in water bath for incubation at 56 °C for 30 min. Later, the solutions were brought to room temperature and repeated centrifugation at 2500 rpm was done for 5 min. The UV-Vis absorbance of the supernatant solutions was recorded at 560 nm. All the experiments were performed in triplicate.

B. Protein denaturation method

All the test compounds were dissolved in small quantity of DMF under ultrasonic conditions for 10-15 min. and further dilutions were carried out with 0.2 M phosphate buffer (pH 7.4). The DMF concentration in the final solution mixtures was less than 2.5 %. 1 ml of prepared test compounds **(3a-j)** of different concentrations, were added to 1ml of albumin solution in phosphate buffer (1mg/ml) and were kept for incubation for about 15mins at 27°±1°C. Further, the reaction mixture was kept in water bath at 60º±1ºC for about 10-20 min. in order to induce the denaturation. The absorbance of the solution was measured by using a UV-Visible spectrophotometer at 660 nm. A comparative analysis with Diclofenac standard and a control (without test compounds) were done by calculating the percentage inhibition of denaturation.

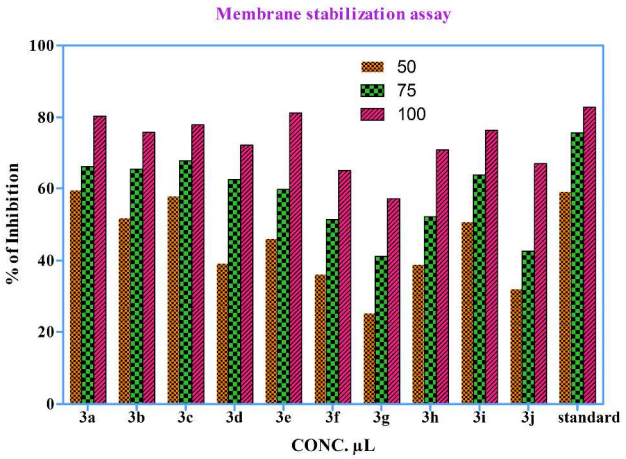


Fig. 2 comparative analysis for anti-inflammatory activities of 1, 6-naphthyridines by membrane stabilization

The percentage inhibition of the membrane stabilization and albumin denaturation activity values (see **Table 3**) were calculated by:

$$\text{Percentage inhibition} = [(\text{Abs}_{\text{control}} - \text{Abs}_{\text{sample}})/\text{Abs control}] \times 100$$

Table 3 Membrane stabilizing and albumin denaturation efficiency of 1, 6-naphthyridines

S. No	Compound	Conc. µg ml^{-1} 50	75	100	IC_{50}
Membrane stabilization method					
1.	**3a**	59.61 ± 1.82	66.05 ± 2.47	80.37 ± 2.57	0.20
2	**3b**	51.89 ± 0.27	65.37 ± 1.31	75.83 ± 2.32	0.80
3	**3c**	57.92 ± 3.17	67.67 ± 0.33	77.92 ± 2.83	0.21
4	**3d**	39.29 ± 2.24	62.44 ± 3.09	72.28 ± 0.15	1.51
5	**3e**	46.16 ±2.35	59.71 ± 4.49	81.24 ± 4.46	1.29
6	**3f**	36.26 ± 3.64	51.37 ± 3.79	64.99 ± 0.95	1.94
7	**3g**	25.24 ± 1.29	41.18 ± 3.05	57.19 ± 1.07	2.55
8	**3h**	39.04 ± 0.61	52.15 ± 3.04	70.67 ± 1.17	1.75
9	**3i**	50.84 ± 2.77	63.73 ± 0.87	76.39 ± 0.36	0.93
10	**3j**	32.15 ± 0.32	42.61 ± 0.49	66.88 ± 1.49	2.16
11	**Standard**	59.18 ± 0.72	75.68 ± 0.99	82.89 ± 1.79	0.095
Albumin denaturation method					
1	**3a**	56.65 ± 1.85	64.12 ± 0.94	77.65 ± 2.29	0.46
2	**3b**	47.97 ± 1.01	62.55 ± 1.52	76.5 ± 1.25	1.13
3	**3c**	54.91 ± 0.44	65.23 ± 1.05	75.31 ± 0.12	0.51
4	**3d**	37.44 ± 0.35	60.04 ± 0.58	69.86 ± 0.93	1.64
5	**3e**	43.99 ± 1.25	57.06 ± 0.11	77.85 ± 0.46	1.43
6	**3f**	34.81 ± 1.66	48.25 ± 1.16	62.7 ± 0.63	2.10
7	**3g**	23.59 ± 1.26	40.16 ± 0.96	55.76 ± 1.11	2.63
8	**3h**	37.13 ± 1.37	50.17 ± 2.53	68.46 ± 0.92	1.79
9	**3i**	48.25 ± 0.49	60.40 ± 0.41	73.99 ± 1.37	1.15
10	**3j**	50.00 ± 0.16	62.75 ± 0.98	73.99 ± 0.99	0.97
11	**standard**	58.42 ± 2.75	73.69 ± 1.49	79.71 ± 1.08	0.06

Each value is the mean ± S. D, standard deviation

3.2 *In vitro* anti-oxidant activity[54]

A. DPPH-scavenging activity

Present study also describes the DPPH (1,1-diphenyl-2-picrylhydrazyl) scavenging activity of the prepared 1, 6-naphthyridines **(3a-j)**. DPPH scavenging assay for the prepared 1, 6-naphthyridine derivatives was checked by the reported method with minor modification. In brief, 1.8 ml of DPPH (10^{-4} M) solution prepared in methanol and was added to 0.2 ml of 1, 6-naphthyridine derivatives and the resulting mixture was allowed for vigorous stirring, and then incubated at 37 $^{\circ}$C for about 30 min. in dark condition. Later, the absorbance for the subsequent mixtures was recorded by using a UV-Visible spectrophotometer at 515 nm. The DPPH scavenging activity of the synthesized 1, 6-naphthyridines was calculated by using the following formula.

$$\text{DPPH-scavenging effect (\%)} = [(A_0 - A_1)/A_0] \text{ X100}$$

Where A_0 and A_1 are the absorbance values of the control and 1, 6-naphthyridine derivatives respectively. Ascorbic acid was used as

standard. All the experiments were carried out in triplicate. The anti-oxidant activity exhibited by the standard and 1,6-naphthyridines at various concentrations is listed in **Table 4. Fig. 3** represents the plot drawn with the inhibition percentage against the various concentrations of the test solutions and the standard, ascorbic acid. All the experiments were repeated thrice to check their accuracy.

Table 4 Anti-oxidant activity of 1, 6-naphthyridines by DPPH scavenging method.

		Conc. µg ml^{-1}			
S. No	**Compound**	**50**	**75**	**100**	**IC_{50}**
1	**Standard**	61.17 ± 1.46	71.09 ± 1.15	86.7 ± 0.98	0.17
2	**3a**	37.69 ± 0.62	47.33 ± 0.93	54.39 ± 0.38	2.43
3	**3b**	55.82 ± 1.89	62.44 ± 0.47	78.68 ± 2.00	0.63
4	**3c**	52.25 ± 1.74	63.52 ± 1.03	76.19 ± 0.19	0.83
5	**3d**	45.24 ± 0.28	60.79 ± 2.57	70.29 ± 0.71	1.29
6	**3e**	54.42 ± 1.27	66.68 ± 0.67	82.08 ± 1.81	0.17
7	**3f**	36.13 ± 2.29	49.08 ± 0.21	57.55 ± 0.45	2.23
8	**3g**	49.65 ± 3.40	54.97 ± 0.55	68.67 ± 2.50	1.18
9	**3h**	32.57 ± 0.81	45.6 ± 1.25	59.5 ± 0.24	2.30
10	**3i**	28.02 ± 2.06	38.59 ± 0.74	53.4 ± 1.58	2.79
11	**3j**	49.67 ± 2.75	51.97 ± 1.04	65.02 ± 1.65	1.27

Each value is the mean ± S. D, standard deviation

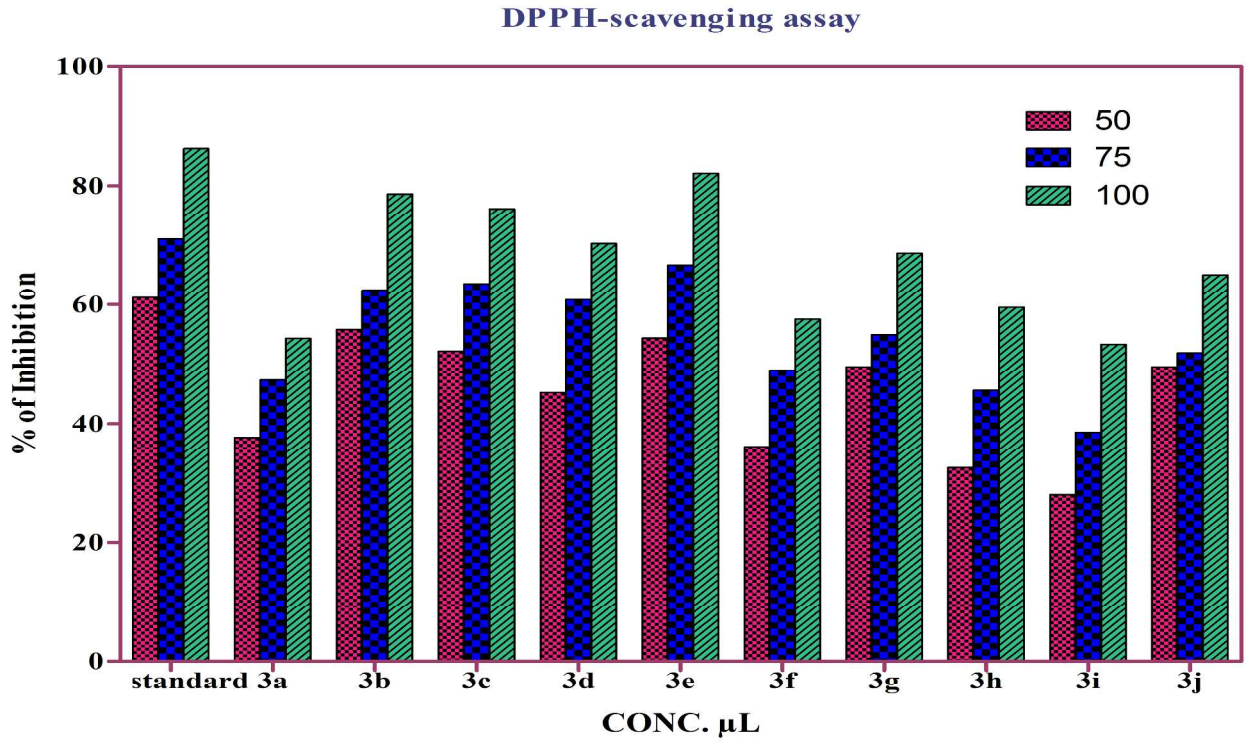


Fig. 3 Comparison of 1, 6-naphthyridines anti oxidant assay percentage inhibition with standard

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Experimental

General procedure for the synthesis of 1, 6-naphthyridines
The general procedure for the preparation of 1, 6-naphthyridines involves the initial drop wise addition of 2 equiv. of malononitrile (2 mmol) to 1 equiv. of ketone (1.0 mmol) **1** in absolute ethanol (20 mL), and then 2 equiv. of pyrrolidine (2 mmol) was added at room temperature. Subsequently, the reaction mixture was kept for reflux and was continuously monitored by using TLC for the complete vanishing of stating material. The solvent in the ensuring mixture was removed by using a rotary evaporator and the obtained residue was purified by column chromatography using silica gel and elution with hexane-ethyl acetate (4:1, 20 %) solvent mixture to afford the 1,6-naphthyridines (**3a-j**).

Conclusion

An efficient, one-pot and multi-component method was reported for the synthesis of 1, 6-napthyridines. A viable mechanistic pathway for the formation of 1, 6-napthyridines was also depicted. *In vitro* anti-inflammatory and 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging activities for all the synthesized 1, 6-naphthyridines were performed and the results clearly show that these compound may play a vital role as leads for the development of potential drug candidates.

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