Research Article

DABCO Promoted One Pot Efficient Synthesis and Antioxidant Activity of 2-Amino-4-phenyl-5-oxo-5, 6dihydro-4H-pyrano [3,2-c]quinoline-3-carbonitrile Derivatives

Sunetra Jadhav[a] ,Reshma patil[a], Digambar Kumbhar[a], Ajinkya Patravale[b], Dattatraya Chandam[b], Madhukar Deshmukh[a,b*]
[a]Department of Agrochemicals and Pest Management, Shivaji University, Kolhapur, M.S., India.
[b]Department of Chemistry, Shivaji University, Kolhapur, M.S., India.
***Corresponding author's E-mail:** Shubhlaxmi111@gmail.com

Accepted on: 12-10-2015; **Finalized on:** 30-11-2015.

ABSTRACT

A convenient one pot synthesis of pyrano quinoline derivatives were developed by three component sequential condensation of 2, 4-dihydroxyquinoline, malononitrile and various substituted aryl aldehydes by using catalytic amount of DABCO in aqueous ethanol and evaluated their *in vitro* antioxidant activity using H_2O_2 and Nitric oxide scavenging assay. The simplicity in synthetic procedure, less pollution, low cost chemicals, short reaction time and easy work-up which proceeded smoothly to provide excellent yields (85-95%) are the main advantage of this protocol. All of the molecules possesses moderate to good antioxidant activity against all scavenging assay.

Keywords: Multicomponent reaction, Green chemistry, Pyrano quinoline derivatives, DABCO.

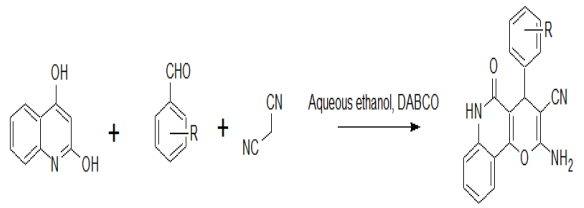
INTRODUCTION

Over the past few decades numerous heterocyclic bio significant molecules have been discovered. Modern era of human being suffering by various microbial infections. Microbes also disturb the metabolic pathways and increases free radicals to cause oxidative stress. There is tremendous growth and the development of pharmacological and agricultural important drugs[1]. In prospect of implementing these types of drugs the synthetic chemists have attracted at large to minimize the cost and time in relevance to their isolation from natural sources. To overcome these aspects and environmental issues there is need to focus on environmentally benign reactions or pathways[2]. The implementation of multi-component reactions (MCRs) is one of the routes to develop such an environmentally benign strategies. MCRs play an important role in heterocyclic chemistry because of its ability to synthesize small drug-like molecules in one step that begins with the use of three or more different starting materials which are mixed together and react in sequence to form a product[3-4]. This MCRs technique in single synthetic operations are widely used in chemical and pharmaceutical combinatorial synthesis[5], which are economically and environmentally advantageous because of their productivity, simple procedures, convergence, atom economy and facile execution. In such a way MCRs are perfectly suited for building complex molecules from readily available starting materials[6]. Thus, the success of combinatorial chemistry in drug discovery is considerably dependent on further advances in heterocyclic MCR methodology and, according to current synthetic requirements, ecologically pure multicomponent procedures are particularly received[7].

It is well known that the compounds with pyran ring are essential nucleus in a number of natural products and play vital role in biochemical process[8-9]. Out of which pyaranoquinoline derivatives constitute parent ring structure of pyranoquinoline alkaloids which is present in plant family Rutaceae[10] which possess broad range of biological activities such as antioxidant, antiplatelet aggregation, antiallergic activity, insecticidal, antifungal, antibacterial, analgesic, antimicrobial, antipyretic, cytotoxic and antihistaminic properties and are used for the treatment of proliferate diseases such as cancer[11-15]. As a result several methods have been developed for the synthetic strategy of these pyranoquinoline derivatives via a one pot three component reaction. As a best of our knowledge there have been found less reports for the synthesis of 2-Amino-4-phenyl-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile derivatives via multicomponent reactions catalyzed by Et3N,[16] KFAl2O3,[17] TEBA(benzyl triethyl ammonium chloride[18], [26] piperidine[19], and ammonium acetate, [BMIm]BF4 ionic liquid[20], and recently one report is found in absence of catalyst[2]. As there is increasing environmental perception in chemical research and industry, these methods have some limitations like use of huge amount of toxic chemicals, metal ions as a catalysts, tedious work up procedures, long reaction time, uses of organic solvents, and create waste. To defeat these problems there is urgent need to develop environmentally safe procedures for the synthesis of pyranoquinoline derivatives.

Recently, organocatalyst has increased more importance because of its novelty of concept and reaction meets the standards of organic synthesis by giving excellent yield.[21] DABCO (Diazabicyclo [2.2.2] octane) is one of the important organocatalyst which has great attention as a weak base, non toxic, recyclable, economical, highly reactive, and commercially available catalyst for various organic synthesis, affording the corresponding products in excellent yields with high selectivity[22].

In continuation of our work to develop a new class of heterocyclic systems which incorporate the pyran moiety[23-25] [30-32] ,we report herein less expensive, much simpler, and more environmentally friendly and in a greener way to develop pyranoquinoline motifs by multicomponent condensation of 2,4 dihydroxyquinoline, malanonitrile and aromatic aldehydes by using aqueous ethanol (ethanol:water) in presence of heterogeneous catalyst DABCO and study their antioxidant activity using H2O2 and Nitric oxide assay.



Scheme I: Synthesis of 2-Amino-4-phenyl-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile **4.**

Experimental:

All the chemicals were purchased from Alfa Aesar and Spectrochem (PVT. Ltd, Mumbai, India) and used without purification. The reaction was monitored by TLC. The desired Structures of all of the compounds were confirmed by their relevant spectral data. The Melting points were determined in open glass capillary tubes were found to be uncorrected. The Compounds were confirmed by IR, 1H NMR and 13C NMR. The IR spectra were recorded on a JASCO FT-IR 4600 spectrum spectrophotometer and the values are expressed as ν max cm^{-1}. The ^{1}H NMR and ^{13}C, DEPT NMR spectra were recorded on Bruker Spectrospin Avance II-300 MHz and 75 MHz spectrophotometer relative to TMS as an internal standard using DMSO-d_6 as a solvent.

General Synthetic Procedure

A mixture of Malononitrile (1 mmol) and aromatic aldehyde (1 mmol), were mixed together in 50 ml round bottom flask under reflux condition to get the knoevenagel product monitored by TLC and then 2,4-dihydroxyquinoline (1 mmol) and DABCO (20%) were added and continued in the reflux condition by using aqueous ethanol as a solvent (5 ml) for 15 min. The progress of the reaction was monitored by TLC using ethyl acetate-petroleum ether (8:2 v/v). After completion, reaction mixture was cooled at room temperature. The product was precipitated in round bottom flask was collected by filtration, washed with ethanol (20 ml). Finally, the crude product was recrystalised with ethanol to obtain the pure product.

Spectral data of synthesized Compounds

4a. 2-Amino-4-(4-chlorophenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

white solid, Yield: 94%: M.p.>300°C ; IR(KBr, vmax cm-1)3464, 3336, 3182, 2191, 1676, 1379, 1117, 1022; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.51 (s, 1H, -CH), 7.24 (m, 8H, Ar-H, -NH_2), 7.50 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 11.70 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 36.60, 56.70, 57.82, 109.31, 112.44, 115.82, 120.13, 122.41, 122.60, 128.64, 129.62, 131.67, 131.92, 138.06, 143.50, 151.91, 159.44, 161.13. Elemental anal. $C_{19}H_{12}ClN_3O_2$, calcd for C 65.24 %, H 3.46 %, N12.01 %. Found: C 65. 20%, H 3.10%, N 11.90%.

4b. 2-Amino-4-(3-chlorophenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

white solid, Yield: 91%: M.p.>300°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.52 (s, 1H, -CH), 7.23-7.34 (m, 5H, Ar-H), 7.51-7.56 (t, 2H, Ar-H), 7.90-7.92 (d, J=6, 2H, Ar-H), 8.22 (s, 1H, Ar-H), 11.75 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 37.00, 47.08, 56.63, 57.64, 109.24, 112.47, 115.84, 120.03, 122.29, 122.34, 126.47, 127.10, 127.74, 130.45, 131.49, 133.51, 138.31, 147.11, 151.93, 159.53, 160.99. Elemental anal. $C_{19}H_{12}ClN_3O_2$, calcd for C 65.24, H 3.46, N 12.01. Found: C 65.21%, H 3.43%, N 11.95%.

4c. 2-Amino-4-(3-nitrophenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

Off white solid, Yield: 89%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.71(s, 1H, -CH), 7.22-7.34 (m, 4H, Ar-H), 7.50-7.59 (m, 2H, Ar-H), 7.70-7.72 (d, 1H, Ar-H), 7.91-7.94(d, J=9, 1H, Ar-H) 8.06 (s, 2H, -NH_2), 11.76 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 37.13, 57.13, 108.81, 112.42, 115.87, 119.85, 122.10, 122.26, 122.38, 122.52, 129.96, 131.51, 134.62, 138.39, 146.82, 148.20, 152.03, 159.67, 160.99. Elemental anal. $C_{19}H_{12}N_4O_4$, calcd for C 63.33 %, H 3.36 %, N15.55 %. Found: C 63.12%, H 3.28%, N 15.49%.

4d. 2-Amino-4-(4-nitrophenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

Off white solid, Yield: 90%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.68 (s, 1H, -CH), 7.29-7.36 (m, 2H, Ar-H), 7.42(s, 2H, Ar-H), 7.49-7.52 (d, J=9, 1H, Ar-H), 7.58-7.63(t, 1H, Ar-H), 7.91-7.94 (d, J=9, 2H, Ar-H)8.15-8.18 (s, 2H, Ar-H -),11.84 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.21, 57.02, 108.68, 112.32, 115.91, 119.92, 122.62, 124.15, 129.31, 131.99, 138.39, 146.79, 152.05, 152.36, 159.40, 160.87. Elemental anal. $C_{19}H_{12}N_4O_4$, calcd for C 63.33 %, H 3.36 %, N15.55 %. Found: C 63.12%, H 3.28%, N 15.49%.

4e. 2-Amino-4-(3-bromophenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3- carbonitrile

white solid, Yield: 91%: M.p.>300°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.52 (s, 1H, -CH), 7.22-7.25 (t, 4H, Ar-H), 7.32-7.37 (t, 4H, Ar-H), 7.51-7.53 (d, J=6, 1H, Ar-H), 7.90-7.92 (d, 2H, Ar-H,) 11.75 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 39.21, 47.15, 56.67, 57.67, 109.24, 112.48, 115.84, 120.00, 122.08, 122.23, 122.23, 122.34, 126.86, 129.97, 130.59, 130.70, 131.43, 138.31, 147.33, 151.93, 159.54, 160.98. Elemental anal. $C_{19}H_{12}BrN_3O_2$, calcd for C 57.89, H 3.07, N 10.66. Found: C 57.81%, H 3.03%, N 10.59%.

4f. 2-Amino-4-(4-bromophenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

white solid, Yield: 93%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.54 (s, 1H, -CH), 6.63 (s, 2H, Ar-H, -NH_2), 7.12-7.16 (t, 3H, Ar-H), 7.25-7.32 (t, 3H, Ar-H), 7.38-7.43 (s, 2H, Ar-H), 7.85-7.87 (d, J= 6, 1H, Ar-H,) 11.55 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 36.60, 57.10, 109.34, 112.54, 115.77, 120.43, 122.09, 129.68, 131.09, 131.34, 138.12, 143.42, 151.93, 159.33. Elemental anal. $C_{19}H_{12}BrN_3O_2$, calcd for C 57.89 %, H 3.07 %, N10.66 %. Found: C 57.76. 20%, H 3.02%, N 10.45%.

4g. 2-Amino-4-(4-cynophenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

Off white solid, Yield: 93%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.63 (s, 1H, -CH), 6.78 (d, 2H, Ar-H) 7.13-7.18 (t, 1H, Ar-H), 7.04 (s, 2H, Ar-H), 7.15-7.20 (t, 1H, Ar-H), 7.30-7.33 (s, 2H, Ar-H), 7.44-7.49 (s, 1H, Ar-H), 7.86-7.89 (s, 1H, Ar-H) 11.73 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 36.83, 58.39, 101.36, 108.40, 108.54, 110.09, 112.51, 115.80, 120.30, 120.99, 122.26, 122.40, 131.61, 138.21, 138.91, 146.47, 147.64, 151.53, 159.41, 160.97. Elemental anal. $C_{20}H_{13}N_3O_4$, calcd for C 66.85 %, H 3.65 %, N 11.69 %. Found: C 66.83%, H 3.61%, N 11.65%.

4h. 2-Amino-4-(4-hydroxyphenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

white solid, Yield: 89%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.40(s, 1H, -CH), 6.64-6.66(d, 1H, Ar-H) 6.99-7.06 (t, 4H, Ar-H), 7.21 (s, 1H, Ar-H), 7.30-7.32 (d, J=6, 1H, Ar-H), 7.49(s, 1H, Ar-H), 11.76 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 36.28, 58.92, 110.51, 112.66, 115.45, 115.73, 120.43, 122.21, 128.79, 131.17, 135.17, 138.05, 151.46, 156.55, 159.38, 161.18. Elemental anal. $C_{19}H_{13}N_3O_3$, calcd for C 68.88 %, H 3.95 %, N 14.49 %. Found: C 68.82%, H 3.88%, N 12.49%.

4i. 2-Amino-5-oxo-4-phenyl-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

white solid, Yield: 87%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.49 (s, 1H, -CH), 7.19-7.21 (d, J=6 Hz, 2H,Ar-H), 7.27-7.29 (d, J=6Hz, 1H, Ar-H), 7.55-7.60 (m, 3H, Ar-H), 7.90(s, 1H, Ar-H), 7.93, (s, 1H, Ar-H), 7.35 (br.s, 2H, -NH_2), 11.78 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 37.19, 58.31, 110.05, 112.53, 115.81, 120.28, 122.26, 122.34, 127.12, 127.83, 128.76, 131.52, 138.25, 144.82, 151.74, 159.47, 160.99. Elemental anal. $C_{19}H_{13}N_3O_2$, calcd for C 72.37 %, H4.16 %, N13.33 %. Found: C 71.61%, H 4.09%, N 12.25%.

4j. 2-Amino-4-(4-methylphenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

white solid, Yield: 90%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.45 (s, 1H, -CH), 7.08 (s, 3H, Ar-H), 7.23-7.34 (m, 2H, Ar-H, -NH_2), 7.55-7.60 (t, 3H, Ar-H), 7.7.89 (s, 1H, Ar-H), 7.91(s, 1H, Ar-H) 11.76 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 21.06, 36.00, 58.41, 110.20, 112.49, 115.80, 120.32, 122.22, 122.41, 127.75, 129.38, 131.61, 136.27, 138.21, 141.90, 151.54, 159.38, 160.93. Elemental anal. $C_{20}H_{15}N_3O_2$, calcd for C 72.94 %, H 4.59 %, N 12.76%. Found: C 72.84%, H 4.30%, N 12.45%.

4k. 2-Amino-4-(furan-2-yl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

Gray, Yield: 88%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.67(s, 1H, -CH), 6.08-6.09 (d, 1H, Ar-H) 6.24 (s, 1H, Ar-H), 7.04 (s, 2H, Ar-H), 7.15-7.20 (t, 1H, Ar-H), 7.30-7.33 (s, 2H, Ar-H), 7.44-7.49 (s, 1H, Ar-H), 7.86-7.89 (s, 1H, Ar-H)11.73 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 30.71, 55.75, 105.85, 107.40, 110.68, 112.62, 115.82, 120.04, 122.17, 122.20, 131.29, 138.18, 141.76, 152.46, 155.60, 160.25, 161.10. Elemental anal. $C_{17}H_{11}N_3O_3$, calcd for C 66.88 %, H 3.63 %, N 13.76 %. Found: C 66.82%, H 3.58%, N 13.69%.

4l. 2-Amino-4-(3-methoxy phenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

white solid, Yield: 88%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.71(s, 3H, -OCH_3), 4.48 (s, 1H, -CH), 6.75 (s, 2H, -NH_2), 7.12-7.22 (m, 3H, Ar-H), 7.31-7.33 (d, 2H, Ar-H), 7.50 (s, 2H, Ar-H), 7.89-7.92(s, 1H, Ar-H) 11.70 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 10.19, 21.33, 50.16, 118.58, 124.41, 130.31, 139.00, 141.93. Elemental anal. $C_{20}H_{12}N_3O_2$, calcd for C 69.56 %, H 4.38 %, N12.17 %. Found: C 69.45%, H 4.28%, N 12.10%.

4m. 2-Amino-4-(2,4-dichlorophenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

white solid, Yield: 89%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.00 (s, 1H, -CH), 7.31-7.36 (m, 5H, Ar-H, -NH_2), 7.55-7.57 (t, 1H, Ar-H), 7.60-7.62 (d, J=6, 2H, Ar-H), 7.90 (s, 1H, Ar-H), 7.92(s, 1H, Ar-H) 11.76 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 34.25, 56.41, 108.40, 112.26, 115.88, 119.70, 122.33, 122.49, 128.19, 129.18, 131.86, 132.10, 132.31, 133.73, 138.42, 141.13, 152.32, 159.36, 160.74. Elemental anal. $C_{19}H_{12}Cl_2N_3O_2$, calcd for C 59.39 %, H 2.89 %, N10.94 %. Found: C 59.26.%, H 2.59%, N 10.74%.

4n. 2-Amino-4-(2-chlorophenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

white solid, Yield: 87%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.02 (s, 1H, -CH), 7.14-7.20 (t, 5H, Ar-H), 7.23-7.28 (t, 1H, Ar-H), 7.35 (s, 2H, Ar-H, -NH_2), 7.52-7.56 (t, 1H, Ar-H), 7.91-7.94 (d, J=9Hz, 1H, Ar-H), 11.68 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 34.47, 56.71, 108.83, 112.38, 115.79, 119.80, 122.26, 122.35, 127.62, 128.44, 129.77, 130.43, 131.40, 132.95, 138.30, 141.83, 152.42, 159.44, 160.94. Elemental anal. $C_{19}H_{12}ClN_3O_2$, calcd for C 65.24 %, H 3.46 %, N12.01 %. Found: C 65.20%, H 3.10%, N 11.90%.

4o. 2-Amino-4-(1,3-benzodioxol-5-yl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

white solid, Yield: 88%: M.p.>300°C ; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.44 (s, 1H, -CH), 5.96-5.97(d, 2H, Ar-H), 6.65-6.68(d, J=9, 1H, Ar-H), 6.74 (s, 1H, Ar-H), 6.80-6.83

(d, J=9, 1H, Ar-H), 7.25-7.29(d, J= 12, 2H, Ar-H), 7.32-7.34 (d, J= 6, 2H, Ar-H), 7.55-7.60 (t, 1H, Ar-H), 7.88-7.91(d, J= 9, 1H, Ar-H), 11.7 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 36.83, 58.39, 101.36, 108.40, 108.54, 110.09, 112.51, 115.80, 120.30, 120.99, 122.26, 122.40, 131.61, 138.21, 138.91, 146.47, 147.64, 151.53, 159.41, 160.97. Elemental anal. $C_{20}H_{13}N_3O_4$, calcd for C 66.85 %, H 3.65 %, N 11.69 %. Found: C 66.83%, H 3.61%, N 11.65%.

4p. 2-Amino-4-(4-hydroxy-3-methoxy phenyl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

White powder, yield:88%: M.p.>300°C; ^{1}H NMR (300 MHz, DMSO-d6): d 3.62 (s, 3H), 4.42 (s, 1H), 6.57 (d, 1H, J = 7.2 Hz), 6.70 (d, J = 7.2 Hz, 1H, Ar-H), 6.84 (s, 1H, Ar-H), 7.15–7.28 (m, 3H, Ar-H), 7.33 (d, J = 7.2 Hz, 1H, Ar-H), 7.54 (t, J = 7.0 Hz, 1H, Ar-H), 7.89 (d, J = 7.0 Hz, 1H, Ar-H), 11.78 (br s, 1H, -NH); ^{13}C NMR (75 MHz, DMSO-d6): d 36.59, 56.10, 58.57, 108.45, 112.45, 110.55, 115.71, 115.99, 119.94, 120.48, 122.15, 122.38, 131.48, 135.35, 138.15, 145.89, 147.62, 151.38, 169.46, 161.11. Elemental Anal. Calcd for $C_{20}H_{15}N_3O_4$: C, 66.48; H, 4.18; N, 11.63. Found: C, 66.44; H, 4.14; N, 11.61.

4q. 2-Amino-4-(thiophen-2-yl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

Brown solid, Yield: 89%: M.p.>300°C ; I^{1}H NMR (300 MHz, DMSO-d_6): δ 4.86 (s, 1H, -CH), 6.87-6.89 (t, 1H, Ar-H) 6.97-6.98 (d, 1H, Ar-H), 7.21-7.23 (d, J=6, 4H, Ar-H), 7.31-7.34 (d, J=9, 1H, Ar-H), 7.47-7.52 (t, 1H, Ar-H), 7.86-7.89 (d, J=9, 1H, Ar-H), 11.80 (br.s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 3204, 58.05, 110.00, 112.56, 115.83, 120.13, 122.21, 122.25, 124.54, 124.63, 127.05, 131.36, 138.17, 149.04, 151.52, 160.06, 161.05. Elemental anal. $C_{17}H_{11}N_3O_2S$, calcd for C 63.54 %, H 3.45 %, N 13.08 %. Found: C 63.51%, H 3.42%, N 13.09%.

4r. 2-Amino-4-(5-nitrothiophen-2-yl)-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

Brown solid, Yield: 90%: M.p.>300°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.94 (s, 1H, -CH), 7.13 (s, 1H, Ar-H), 7.27-7.37 (t, 2H, Ar-H), 7.56 (d, 2H, Ar-H), 7.88-7.91 (d, J=9, 2H, Ar-H), 8.22 (s, 1H, Ar-H) 11.98 (br. s, 1H, -NH) ^{13}C NMR (75 MHz, DMSO- d_6): δ 33.06, 44.75, 55.72, 108.20, 112.34, 116.01, 119.54, 122.46, 125.27, 129.90, 131.87, 138.41, 149.76, 158.04, 160.48, 160.90. Elemental anal. $C_{17}H_{10}N_4O_4S$, calcd for C 55.73, H 2.75, N 15.29. Found: C 55.71, H 2.73, N 15.23.

Antioxidant activity

Hydrogen peroxide scavenging assay[26]

This method is based on the ability of a compound to convert hydrogen peroxide to water. A 40 mM solution of hydrogen peroxide was prepared in saline phosphate buffer (pH 7.4). 100 µl DMSO solutions of the test compounds or standards at the concentrations of (100 µg/ml) were separately added to 2 ml of the prepared hydrogen peroxide solution and the absorbance was measured at 230 nm after 10 min against a blank solution. The blank solution was composed of 100 µl DMSO solutions of test compounds or standards and 2 ml of saline phosphate buffer. The hydrogen peroxide scavenging activity for compounds and standards was calculated using the following equation:

H_2O_2 scavenging activity (%) = [(Ac-At) / Ac] × 100

Where, Ac is the absorbance of the control and At is the absorbance of the tested compounds or standards. Gallic acid at the concentration range of (100 µg/ml) was used as the standard.

Nitric oxide scavenging activity[27]

The reaction mixture (6 ml) containing sodium nitroprusside (10 mM, 4 mL), phosphate buffer saline (pH 7.4, 1 ml) and test samples or standard, ascorbic acid solution in dimethyl sulphoxide (1 mL) at concentration (100 µg/ ml) was incubated at 25°C for 150 min. After incubation, 0.5 mL of reaction mixture containing nitrite ion was removed, 1 ml of sulphanillic acid reagent was added to this, mixed well and allowed to stand for 5 min for completion of diazotization. Then, 1 ml of naphthyl ethylene diamine dihydrochloride was added, mixed and allowed to stand for 30 min in diffused light. A pink colored chromophore was formed. The absorbance was measured at λ 640 nm 24 using spectrophotometer.

% of scavenging= [(A control – A sample) / A control] ×100

Where A control is the absorbance of the control reaction (containing all reagents and Ascorbic acid), A sample is the absorbance of the test compound (containing all reagents and test compound). Tests were carried out in triplicate. The results obtained from antioxidant assay shows (Table.1.4 and Fig1.1)

RESULTS AND DISCUSSION

The high bioactive potential of pyranoquinoline derivatives enthused us to develop new methodology for the synthesis of pyranoquinoline derivatives. At the commencement, a model reaction of 4-chlorobenzaldehyde (1mmol), malononitrile (1mmol) and 2,4- dihydroxyquinoline (1mmol) was carried out as a trial experiment in the absence of catalyst under various conditions, however it has been found that the expected results were not obtained since reaction was not proceed beyond the knoevenagel condensation even until 12h at room temperature (Table 1, entry1-6). Later on the reaction was performed at reflux condition in absence of catalyst reaction was proceed but the product yield were minimum and time consuming (Table no 1) In the pursuit of suitable catalytical condition for this selective transformation, we employed a variety of several catalysts such as triethylene amine, KOH and DABCO. Further to evaluate the solvent effect in order to establish appropriate reaction conditions we screened different catalyst with several solvent systems depicted in Table 1.

Results summarized from table 1 clearly suggest that, the aqueous ethanol was found to be the best solvent and DABCO found to be the best catalyst for this organic reaction, providing 94% of the product within 15 min (Table 1, entry 15). The reaction was subsequently monitored by thin layer chromatography (TLC). The obtained product was recrystalised from ethanol to give pure product and further analyzed by relevant spectroscopic data. The IR, ^{1}H NMR and ^{13}C NMR data of 2-Amino-4-phenyl-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile derivatives were in good agreement with the proposed structure. The IR spectrum of 7- 2-Amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one shows absorption at 3465, 3336, 3182, 2091, 1675, 1279, 1115, 1015 whereas the ^{1}H NMR of the same compound shows singlet at 4.51 δ due to methine proton, broad singlets at 11.70 due to the –NH protons and eight aromatic protons as multiplets 7.24-7.91d. The ^{13}C NMR spectrum of the same compound exhibits signals at 161.13 of C–NH2 and the remaining aromatic carbon signals were observed at δ 36.60, 56.70, 57.82, 109.31, 112.44, 115.82, 120.13, 122.41, 122.60, 128.64, 129.62, 131.67, 131.92, 138.06, 143.50, 151.91, 159.44, in the product verifies the formation of the desired structure (see Supporting Information). These initial results inspired us to study this reaction in detail.

After the primary success in the model reaction, the catalytic efficiency of DABCO had been studied with respect to quantity used, the same reaction was extended with varying amount of DABCO in aqueous ethanol. It has been observed that 20% of catalyst is sufficient for this conversion. The results are summarized in figure 1.

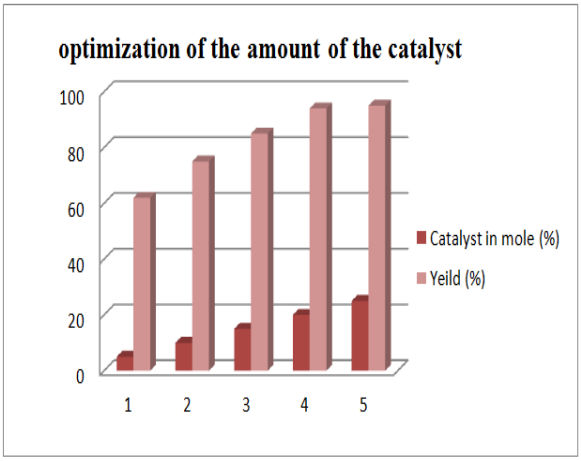


Figure 1: Optimization of the amount of the catalyst

These optimistic results inspired us to check the applicability of the present protocol to get a new library of 2-Amino-4-phenyl-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile derivatives by using experimentally designed optimum conditions with various substituted aldehydes (Scheme 2) with electron donating or electron withdrawing substituent. Aromatic aldehydes with electron withdrawing groups gave better yield of the product in shorter time as compared with an electron donating groups. This result shown that this new methodology is very useful for the synthesis of said compound; all the aldehyde precursors gave very good yields irrespective of their substitution (Table 3). Overall very good to excellent yields of the desired pyranoquinoline derivatives were obtained.

Table 1: Optimization of reaction conditions for the synthesis of 2-Amino-4-phenyl-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

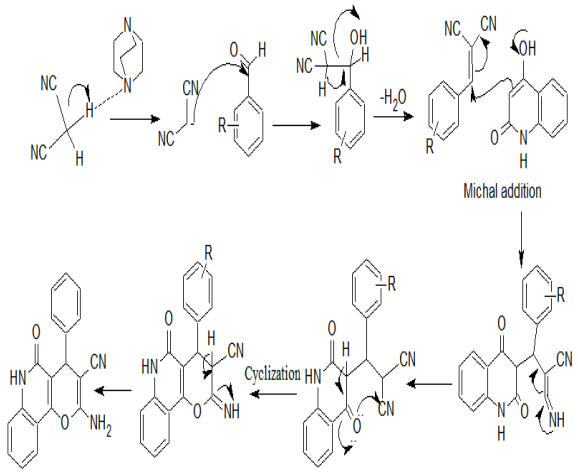
Entry	Solvent	Temperature	Catalyst (20 mole %)	Time (hr)	Yield(%)
1	Water	RT	--	12	--
2	Ethanol	RT	--	12	--
3	Water:Ethanol(1:1)	RT	--	12	--
4	Water	Reflux	--	10	35
5	Ethanol	Reflux	--	10	50
6	Water:Ethanol(1:1)	Reflux	--	10	65
7	Water	Reflux	Triethylene amine	5	50
8	Ethanol	Reflux	Triethylene amine	5	55
9	Water:Ethanol(1:1)	Reflux	Triethylene amine	5	65
10	Water	Reflux	KOH	2.5	55
11	Ethanol	Reflux	KOH	2.5	67
12	Water:Ethanol(1:1)	Reflux	KOH	2.5	72
13	Water	Reflux	DABCO	2.5	79
14	Ethanol	Reflux	DABCO	1	89
15	Water:Ethanol(1:1)	Reflux	DABCO	15(min)	94

Table 2: DABCO catalysed synthesis of novel 2-Amino-4-phenyl-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile

Entry	Compound	Aldehyde	Time (min)	Yield(%)	MP(^{0}C)
1	4a	4-ClC6H4	15	94	>300
2	4b	3-ClC6H4	15	91	>300
3	4c	3-NO2C6H4	15	89	>300
4	4d	4-NO2C6H4	10	90	>300
5	4e	3-BrC6H4	15	91	>300
6	4f	4-BrC6H4	10	93	>300
7	4g	4-CNC6H4	10	93	>300
8	4h	4-OHC6H4	20	89	>300
9	4i	HC6H4	20	87	>300
10	4j	4-CH_3C6H4	10	90	>300
11	4k	C5H4O2	20	88	>300
13	4l	3-OCH3C6H4	25	88	>300
15	4m	2,4-Cl2C6H3	20	89	>300
16	4n	2-ClC6H4	25	87	>300
17	4o	C8H6O3	20	88	>300
18	4p	C8H8O3	20	88	>300
19	4q	C4H4S	15	89	>300
20	4r	C5H3NO3S	15	90	>300

Table.3: Antioxidant activity of -Amino-4-phenyl-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile derivatives

Entry	Comp code	Nitric oxide radical scavenging activity (%of Inhibition) 100 µg/ml	H2O2 radical scavenging activity (%of Inhibition) 100 µg/ml
1	4a	51.05	51.06
2	4b	49.46	49.21
3	4c	43.52	44.25
4	4d	48.14	45.01
5	4e	45.10	46.18
6	4f	42.05	42.78
7	4g	43.02	45.01
8	4h	52.11	52.36
9	4i	46.15	45.02
10	4j	41.36	43.01
11	4k	43.01	43.56
13	4l	51.25	52.20
15	4m	47.56	48.21
16	4n	45.26	45.90
17	4o	48.09	49.15
18	4p	48.84	49.07
19	4q	47.08	47.95
20	4r	49.14	49.85
21	Ascorbic acid	56.18	60.48
22	Gallic acid	51.70	57.04



Scheme II: Plausible mechanism of the reaction

All these newly synthesized compounds have been interpreted on the basis of their relevant spectroscopic data likes IR, ^{1}HNMR, ^{13}C and mass spectra. The plausible mechanism for the formation of 2-Amino-4-phenyl-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile derivatives is depicted in Scheme-II. Initial Knoevenagel condensation of malononitrile (I) and aromatic aldehydes (II) followed by Michael addition of 2,4-dihydroxyquinoline gives an intermediate (IV).

The intermediate (IV) subsequently under goes cyclization followed by dehydration offering the desired product.

Antioxidant activity

Due to their unique flexibility and derivatizations the structural elements of these chains are correlates with such type of activities.

To this end, a number of radical scavenging tests were carried out against Nitric oxide radical scavenging and H_2O_2 assay assay.

The results demonstrate that compounds 4a,4b,4d,4h,4l and 4r of pyrano quinoline motifs possesses significant activity at 100µg/ml while other shows moderate activity as compared with standards (Table.3 and Fig.2)

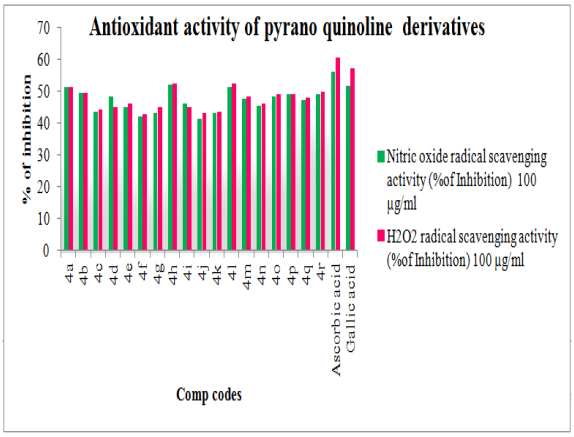


Figure 2: Antioxidant activity of 2 -Amino-4-phenyl-5-oxo-5, 6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile derivatives

CONCLUSION

In conclusion, a simple, easy-going, efficient and environmentally benign method for the synthesis of a series of potential biological active compounds 2-Amino-4-phenyl-5-oxo-5,6 dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile derivatives has been developed using DABCO as a green catalyst in aqueous ethanol. The synthesized all molecules possess good antioxidant activity at 100 µg/ml, which may be taken into consideration in the design of new antibiotic agents.

REFERENCES

1. B. Chandrakantha , A. M. Isloor , P. Shetty , H. Kun Fun, G. Hegde Synthesis and Biological Evaluation of Novel Substituted 1,3,4-Thiadiazole and 2,6-Di Aryl Substituted Imidazo [2,1-b][1,3,4]Thiadiazole Derivatives. European Journal of Medicinal Chemistry. 71, 2014, 316-323.

2. Meng-Jian Yao, Zhi Guan, and Yan-Hong He Simple, Catalyst-Free, One-Pot Procedure for the Synthesis of 2-Amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-oneDerivatives Synthetic Communications. 43, 2013, 2073– 2078.

3. Dömling, A.; Ugi, I. Angew. Multicomponent reaction Chem., Int. Ed. 39, 2000, 3168–3210.

4 Augusto L. Xavier , Alfredo M. Simas , Emerson P. da S. Falcão , Janaína V. dos Anjos ChemInform Abstract: Antinociceptive Pyrimidine Derivatives: Aqueous Multicomponent Microwave-Assisted Synthesis. Tetrahedron Letters. 54 , 2013, 3462– 3465

5 Abbas Ali Esmaeili, SaeidAmini-Ghalandarabad, FaribaMesbah, MasoudTasmimi MohammadIzadyar, Ali Reza Fakharic, Ali Reza Salimia (Efficient synthesis of novel spiro[indole-3,6'- pyrano[2,3-d][1,3]thiazolo[3,2-a]pyrimidine derivatives through an organobase-catalyzed, three- component reaction Tetrahedron, 71, 16, 2015, 2458-2462.

6 Zhu, J.; Bienayme, H. Multicomponent Reactions; Wiley-VCH: Weinheim, Germany, 2005.

7 Michail N. Elinson, Alexey I. Ilovaisky, Valentina M. Merkulova, Dmitry V. Demchuk, Pavel A. Belyakov, Yuri N. Ogibin, Gennady I. Nikishin, The electrocatalytic cascade assembling of isatins, malononitrile and N-alkyl barbiturates: An efficient multicomponent approach to the spiro[indole-3,5′-pyrano[2,3-d]pyrimidine] framework, ElectrochimicaActa .53, 2008, 8346–8350.

8 Ben Said, A., Romdhane, A., Nicolas, E., Touboul, D., Ben Jannet, H., Synthesis of Novel Fused Coumarine and naphtho[2,1-b]pyrano[3,2- e][1,2,4] triazolo[1,5-c]pyrimidine Derivatives. Lett.Org. Chem. 10 (3), 2013, 185–190.

9 Romdhane, A., Gallard, J.F., Hamza, M.A., Ben Jannet, H. Synthesis of New Phosphonate Derivatives of Naphtho[2,1-b[Pyran]3,2-e][1,2,4]Triazolo [1,5-c]Pyrimidines. Phosphorus, Sulfur Silicon Relat. Elem. 187, 2012, 612–618.

10 T Dhanabal, T Suresh, P.S. Mohan, Synthesis of new 1, 10-diethoxy-1H-pyrano[4, 3- b]quinolines and their antibacterial studies Indian journal of Chemistry. 45B, 2006, 523-525.

11 Chen, I. S.; Tsai, I. W.; Teng, C. M.; Chen, J. J.; Chang, Y. L.; Ko, F. N.; Lu, M. C.; Pezzuto, J. M. Pyranoquinoline alkaloids from zanthoxy lumsimulans. Phytochem. 46, 1997, 525–529.

12 Wabo, H. K.; Tane, P.; Connolly, J. D.; Okunji, C. C.; Schuster, B. M.; Iwu, M. M. Tabouensinium chloride, a novel quaternary pyranoquinoline alkaloid from Araliopsis tabouensis. Nat. Prod. Res. 19, 2005, 591–595

13 Michael, J. P. Quinoline, quinazoline, and acridone alkaloids. Nat. Prod. Rep. 2002, 19, 742–760; (b) Michael, J. P. Quinoline,

quinazoline, and acridone alkaloids. Nat. Prod. Rep. 2003, 20, 476–493; (c) Michael, J. P. Quinoline, quinazoline, and acridone alkaloids.Nat. Prod. Rep. 2004, 21, 650–668; (d) Michael, J. P. Quinoline, quinazoline, and acridone alkaloids. Nat. Prod. Rep. 22, 2005, 627–646.

14 (a) Nahas, N. M.; Abdel-Hafez, A. A. Synthesis of Certain Fused Thienopyrimidines of Biological Interest, Heterocycl. Commun. 11, 2005, 263–272; (b) Amin, K. M. New pyrano [3,2-f]quinolines of possible H1–antihistamine and mast cell stabilizing properties,Egypt. J. Pharm. Sci. 34, 1993, 741–750; (c) Magesh, C. J.; Makesh, S. V.; Perumal, P. T. Highly diastereo selective inverse electron demand (IED) Diels–Alder reaction mediated by chiral salen–AlCl complex: the first, target-oriented synthesis of pyranoquinolines as potential antibacterial agents, Bioorg. Med. Chem. Lett. 14, 2004, 2035–2040.

15 Schiemann K.; Emde U.; Schlueter T.; Saal C.; Maiwald M. WO Patent 2007147480A2, 2007, Chem. Abstr. 148, 2007, 85962.

16 Tang Y.; Oppenheimer J.; Song Z.; You L.; Zhang X.; Hsung R. P. Strategies and approaches for constructing 1-oxadecalins, Tetrahedron, 62, 2006, 10785–10813; (b) McKee, T. C.; Fuller, R. W.; Covington, C. D.; Cardellina, J. H., II; Gulakowski, R. J.; Krepps, B. L.; McMahon, J. B.; Boyd, M. R. New Pyranocoumarins Isolated from Calophyllum lanigerum and Calophyllum teysmannii, J. Nat. Prod. 59, 1996, 754–758 (c) McKee, T. C.; Covington, C. D.; Fuller, R. W.; Bokesch, H. R.; Young, S.; Cardellina, J. H., II; Kadushin, M. R.; Soejarto, D. D.; Stevens, P. F.; Cragg, G. M.; Boyd, M. R. Pyranocoumarins from Tropical Species of the Genus Calophyllum: A Chemotaxonomic Study of Extracts in the National Cancer Institute Collection,J. Nat. Prod. 61, 1998, 1252–1256; (d) Wu, S.-J.; Chen, Alkaloids from Zanthoxylum simulans, I.-S.Phytochemistry 34, 1993, 1659–1661; (e) Jung, E. J.; Park, B. H.; Lee, Y. R. Environmentally benign, one-pot synthesis of pyrans by domino Knoevenagel/6π-electrocyclization in water and application to natural products,Green Chem. 12, 2010, 2003–2011.

17 Min Lei, Lei Mab, Lihong Hu. A green, efficient, and rapid procedure for the synthesis of 2-amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one derivatives catalyzed by ammonium acetate, Tetrahedron Letters, 52, 2011, 2597–2600.

18 Wang X. S.; Zheng Z. S.; Li Y. L.; Shi D. Q.; Tu S. J.; Wei X. Y.; Zong Z. M. Synthesis of 2-amino-4-aryl-5,6-dihydro-4H-pyrano[3,2-c]quinolin-5-one derivatives in water. Chin. J. Org. Chem. 26, 2006, 228–232.(Q-M)

19 Ajmal R. Bhat, Aabid H. Shalla, Rajendra S. Dongre . Synthesis of new annulated pyrano[2,3-d]pyrimidine derivatives using organo catalyst (DABCO) in aqueous media, Journal of Saudi Chem. Society, 2014.

20 (a) I.V. Magedov, M. Manpadi, E. Rozhkova, N.M. Przheval'skii, S. Rogelj, S.T. Shors, W.F.A. Steelant, S. Van Slambrouck, A. Kornienko. Structural simplification of bioactive natural products with multicomponent synthesis: Dihydropyridopyrazole analogues of podophyllotoxin, Bioorg. Med. Chem. Lett. 17, 2007, 1381-1385. (b) I.V. Magedov, M. Manpadi, M.A. Ogasawara, A.S. Dhawan, S. Rogelj, S. Van slambrouck, W.F.A. Steelant, N.M. Evdokimov, P.Y.Uglinskii, E.M. Elias, E.J. Knee, P. Tongwa, M. Yu. Antipin, A. Kornienko, Structural Simplification of Bioactive Natural Products with Multicomponent Synthesis. 2. Antiproliferative and Antitubulin Activities of Pyrano[3,2-c]pyridones and Pyrano[3,2-c]quinolones.J. Med.Chem. 51, 2008, 2561-2570. (c) X. Fan, D. Feng, Y. Qu, X. Zhang, J. Wang, P.M. Loiseau, G. Andrei, R. Snoeck, E. Clercq. Practical and efficient synthesis of pyrano[3,2-c]pyridone, pyrano[4,3-b]pyran and their hybrids with nucleoside as potential antiviral and antileishmanial agents, Bioorg. Med. Chem. Lett. 20, 2010, 809-813.

21 Shubha Jain, Pradeep K. Paliwal, G. Neelaiah Babu, Anjna Bhatewara. DABCO promoted one-pot synthesis of dihydropyrano(c)chromene and pyrano[2,3-d]pyrimidine derivatives and their biological activities, Journal of Saudi Chemical Society, 18, 2014, 535–540.

22 Da-Zhen X., Yingjun L., Sen S., Yongmei W. A simple, efficient and green procedure for Knoevenagel condensation catalyzed by [C4dabco][BF4] ionic liquid in water, Green Chem. 12, 2010, 514–517.

23 Patil D.; Chandam D.; Mulik A.; Patil P.; Jagadale S.; Deshmukh M. Multicomponent synthesis of highly functionalized piperidines using sulfamic acid as a heterogeneous and cost effective catalyst., Indian J Chem, 54B, 2015, 545-550.

24 Mulik A.; Chandam D.; Patil P.; Patil D.; Jagadale S.; Sankpal S.; Deshmukh M. Polymer-Supported Sulfonic Acid-Catalyzed Candid Synthesis and Photophysical Properties of 2H-indazolo[2,1-b]phthalazinetriones, J. Heterocycls. Chem. 52, 2015, 931.

25 Patravale A. A.; Gore A. H.; Patil D. R.; Kolekar G. B.; Deshmukh M. B.; Anbhule P. V. Trouble-Free Multicomponent Method for Combinatorial Synthesis of 2-Amino-4-phenyl-5-H-indeno[1,2-d]pyrimidine-5-one and Their Screening against Cancer Cell Lines, Ind. Eng. Chem. Res. 53, 2014, 16568–16578.

26 Jayaprakasha GK, Jaganmohan RL, Sakariah KK, Bioorg. Med. Chem, 12, 2004, 5141-5146.

27 Marcocci L, Packer L, Droy-lefaix MT, Sekaki A, Gondes-albert M, Methods Enzymol, 234 ,1994, 462-473.

Source of Support: Nil, **Conflict of Interest:** None.

Corresponding Author's Biography : Prof. M.B. Deshmukh

Prof. Deshmukh did B.Sc, M.Sc & Ph.D. from Shivaji University & guided 31Ph.D, 11 M.Phil's and published 264 papers in reputed good impact factored journals. He was Post-Doctoral fellow 1993-94 in University of Graz, Austria & visiting Professor, Hanyang University, Korea during March 2010. He was handled multiple UGC, DST projects at University.