Microwave Assisted Green Catalyzed One-pot Synthesis, Characterization, and Biological Significance of Hexahydroquinolines

Manoj P. Palve[a], Amol V. Sapkal[b], Ajeet A. Yelwande[a], Pritam A. Mule[a], and Rajita D. Ingle[c]*
[a] *Indraraj Arts, Commerce and Science College, Sillod, Chh. Sambhajinagar, Maharashtra, India.*
[b]*Phulsing Naik Mahavidyalaya, Pusad Dist:Yavatmal, Maharashtra, India.*
[c]*Department of Chemistry, Deogiri College, Chh. Sambhajinagar, Maharashtra, India*

Abstract: A convenient method for the synthesis of hexahydroquinoline through one-pot four component approach using aromatic aldehydes, dimedone, malononitrile and ammonium acetate by using green catalyst under microwave irradiation. Shorter reaction time, high atom economy, easy work up and purification of products are the crucial features of this methodology. These chemicals are easily modifiable to elicit desirable features in the target product by choosing the right precursors. The protocol has been utilized mild reaction conditions, excellent yield, shorter reaction time and simple workup procedure. The synthesized derivatives were obtained in 82-96% yields and were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectra and biological significance.

Keywords: Multicomponent reaction, Microwave irradiation, Hexahydroquinoline, Methanesulphonic acid.

I. INTRODUCTION

A chemical reaction known as a multicomponent reaction (MCRs) occurs when three or more reactants combine in a single reaction vessel to create a product that contains components from each reactant. It could provide facile, efficient and practical methods in modern medicinal chemistry for the construction of molecular complexity and structural diversity. Multi-component reactions are simple to design, efficient, eco-friendly, and can create target compounds using various elements in one-pot processes with straightforward procedures.[1] The use of microwave irradiation in organic synthesis has become a potent and adaptable approach that is transforming the way chemical processes are carried out in lab settings. In contrast to conventional heating techniques, which depend on outside heat sources like heating mantles or oil baths, microwave irradiation heats the reactants directly using electromagnetic waves. This technique frequently produces cleaner reactions with fewer byproducts while also greatly increasing reaction rates and yields.[2]

A significant class of heterocyclic compounds known as hexahydroquinolines are distinguished by a partly hydrogenated quinoline ring structure. This structural motif consists of a fused bicyclic system in which the other ring is a nitrogen-containing saturated six-membered ring and the first ring is a benzene ring. Numerous natural products and synthetic pharmaceuticals use hexahydroquinoline as a well-known structural scaffold due to its wide range of biological characteristics.[3] They are employed as antimicrobial,[4] anti-inflammatory,[5] antioxidant, [6] anti-anaphylactic, and diuretic agents,[7] anticancer,[8] insecticidal,[9] antibacterial and antifungal properties.[10] Several homogeneous and heterogeneous catalysts have been utilized in the synthesis of substituted hexahydroquinoline derivatives. Among them, some of mentioned here Fe_3O_4@B-MCM-41,[11] iodotrimethylsilane,[12] triethylamine,[13] $Bi(NO_3)\cdot 5H_2O$,[14] nano TiO_2,[15] Pd nanoparticle,[16] K_2CO_3,[17] tetrabutylammonium hexatungstate,[18] AcOH,[19] Yb $(OTf)_3$,[20] Scolecite,[21] CAN,[22] and Sc $(OTf)_3$.[23] However, many of the reported methods still face several challenges, including prolonged reaction times, low yields, harsh reaction conditions, the use of hazardous solvents and catalysts.

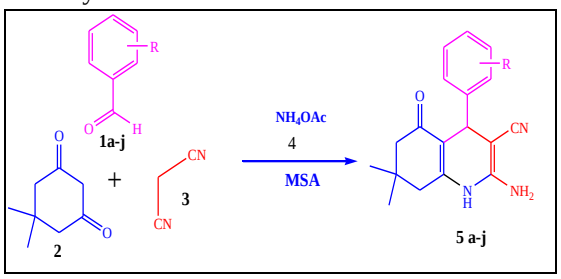
Therefore, there is a need to develop an environmentally friendly and efficient method for synthesizing hexahydroquinoline derivatives. So, our aim of this work is to present eco-friendly, atom-

economical and highly effective protocol. This approach involves a tandem synthesis of hexahydroquinoline derivatives through a four-component condensation of dimedone, aryl aldehydes, malononitrile, and an excess of ammonium acetate and a catalytic quantity of methane sulphonic acid (MSA) to accomplish this. Our approach was quick, easy, clear-cut, elegant, and efficient. (Scheme 1). Methane sulfonic acid (MSA) is an alkanesulfonic acid with the chemical formula CH_3SO_3H. It is a strong acid with a pKa of 1.9. MSA is biodegradable and does not release toxic gases, making it an environmentally friendly choice. Due to these properties, MSA is often favored by chemists for use in organic synthesis.[24]

II. EXPERIMENTAL

MATERIAL AND METHODS

All the chemicals and synthetic grade reagents were procured from Sigma Aldrich India and Merck chemicals. They were used without further purification. Melting points were recorded in open capillaries using a Buchi melting-point B-540 apparatus. ^{1}H NMR spectra were obtained on a Bruker instrument (400 MHz) and chemical shifts are reported in δppm. Mass spectra were measured using high-resolution ESI–MS (DFS) Thermo spectrometers (70 eV). ^{13}C NMR was recorded on a Bruker DRX 100 MHz Spectrometer Microwave irradiation was carried out in a Microwave Oven, Model No. MS2044DB DB1QILN (2450 MHz, 1050 W) equipped with Erlenmeyer flask.



Scheme 1: Synthesis of hexahydroquinoline derivatives using green catalyst under microwave irradiation.

GENERAL PROCEDURE FOR THE SYNTHESIS OF HEXAHYDROQUINOLINE AND ITS DERIVATIVES (5a-j)

A mixture of substituted aromatic aldehydes (0.01 mol), dimedone (0.01 mol), malononitrile (0.01 mol), ammonium acetate (0.02 mol), in the presence of catalytic amount of methanesulphonic acid in ethanol under irradiated in microwave oven in an Erlenmeyer flask and irradiated until completion of the reaction. Thin layer chromatography (TLC) with ethyl acetate: n-hexane (2:8) eluent system was used to check the reaction progress. Once the reaction was complete, as shown by TLC, the reaction mixture was poured in crushed ice and filtered it. The residue was then recrystallized from ethanol to obtain the purified product. The entire product was characterized by physical constant and spectroscopic techniques compared with the standard method.

III. RESULTS AND DISCUSSION

We present a novel synthetic strategy for the synthesis of substituted hexahydroquinoline derivatives using benzaldehyde (0.01 mol), dimedone (0.01 mol), malononitrile (0.01 mol), and ammonium acetate (0.02 mol) as model substrates, with a catalytic amount of methanesulphonic acid (MSA) in ethanol under microwave irradiation. Initially, the reaction was first attempted without any catalyst, but it did not proceed (Table 1, Entry 1). Introducing a trace amount of catalyst (2 mol% - 4 mol%) allowed the reaction to proceed, although the desired product was not obtained (Table 1, Entries 2 & 3).

Table 1: Optimization of catalyst concentration for the synthesis of hexahydroquinoline under M.W. Irradiation.[a]

Entry	Catalyst Mol %	Time in Min	Yield (%)[b]
1	0	25	Trace
2	2	9	75
3	4	5	90
4	6	4	96
5	8	5	83
6	10	10	69

[a]Reaction conditions: Benzaldehyde (0.01 mol), dimedone (0.01 mol), malononitrile (0.01 mol), and ammonium acetate (0.02 mol), catalyst (6 mol%) & ethanol 10 mL. [b]Isolated yields. [b]Isolated yields.

Optimization with 6 mol% of catalyst under microwave irradiation resulted in the desired product being achieved in excellent yield (89%) (Table 1, Entry 4). Increasing the catalyst amount beyond this level led to a slower reaction rate and a reduced yield

of the desired product (Table 1, Entries 5 & 6). Next, we focused on finding the optimal solvent for synthesizing the target molecule. To this end, we performed the model reaction in the presence of various solvents, and the results are summarized in Table 2. Obviously, the highest yield was observed while using ethanol as a solvent.

Table 2. Solvents effect on the Hexahydroquinoline synthesis[a]

Entry	Solvent	Time (Min)	Yield (%)[b]
1	Ethanol	4	96
2	Methanol	7	89
3	Acetonitrile	14	81
4	THF	17	73
5	DMF	18	76
6	1,4-dioxane	21	65

[a]All reaction were carried out using MSA catalyst under MWI. [b]Isolated yields.

The optimized tandem methodology tolerated a wide spectrum of aldehydes with good to excellent yields of the targeted molecules. From Table 3 it is evident that the reaction proceeded smoothly for both electron rich and electron deficient aromatic aldehydes. All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, LC–MS and by elemental analysis and well matched with literature reported compound.

Spectroscopic Characterization of the synthesized derivatives.

2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5a)

IR(KBr cm^{-1}): 3399, 3315, 3256, 2934, 2162, 1651, 1622, 1493; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.97(s, 3H, CH_3), 1.0 (s, 3H, CH_3), 1.92-2.14 (dd, 2H, J=15 Hz, CH_2), 2.34- 2.54 (dd, 2H, J=17.6, CH2), 4.37 (s, 1H, CH), 5.91 (s, 2H, NH_2), 6.93-7.31 (m, 5H, Ar-H), 7.22-7.52 (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.3, 27.3, 31.4, 42.5, 53.6, 58.0, 112.7, 115.3, 122.9, 123.2, 125.2, 127.4, 133.4, 145.5, 150.0, 164.2, 199.2.; ESI-MS(m/z): 294.3 $[M+H]^+$

2-Amino-4-(4-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo1,4,5,6,7,8-hexahydroquinoline (5b)

IR(KBr cm^{-1}): 3373, 3315, 3173, 2965, 2673, 1664, 1495, 1376; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.91 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.91-2.11,3.72-3.84 (s, 3H, -OCH_3) (dd, 2H, J=15 Hz, CH_2), 2.32-2.43 (dd, 2H, J=17.0, CH2), 4.45 (s, 1H, CH), 5.90 (s, 2H, NH_2), 6.65-7.02, (dd , 2H Ar-H), 6.65-7.05, (dd, 2H, Ar-H), 7.10-8.6, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.3, 31.7, 37.6, 45.2, 55.5, 60.5, 112.0, 122.9, 125.9, 127.2, 131.4, 132.4, 151.5, 154.0, 165.2, 196.0; ESI-MS(m/z): 324 $[M+H]^+$

2-Amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo1,4,5,6,7,8-hexahydroquinoline (5c)

IR(KBr cm^{-1}): 3495, 3321 and 3223, 2174, 1690, 1440, 1330, 745; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.92 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.93-2.30 (dd, 2H, J=15 Hz, CH_2), 2.40-2.95 (dd, 2H, J=17.0, CH_2), 4.35 (s, 1H, CH), 5.78 (s, 2H, NH_2), 7.31, (d, 2H, J=8.0 Hz, Ar-H), 7.15, (d, 2H, J=8.0 Hz, Ar-H), 7.15-8.5, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.2, 31.3, 38.4, 43.3, 51.5, 57.3, 111.6, 115.4, 117.7, 130.9, 134.2, 150.5, 161.0, 197.4.; ESI-MS(m/z): 327 $[M+H]^+$

2-Amino-4-(3-nitrophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5d)

IR(KBr cm^{-1}): 3392, 3330, 3222, 2178, 1658, 1599 cm-1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.04 (s, 1H, NH), 8.04 (d, 1H, J = 7.6 Hz, ArH), 7.93 (s, 1H, ArH), 7.64-7.57 (m, 2H, ArH), 5.94 (s, 2H, NH2), 4.50 (s, 1H, CH), 2.46 (d, 1H, J = 17.2 Hz, CH2), 2.35 (d, 1H, J = 17.2 Hz, CH2), 2.20 (d, 1H, J = 16.0 Hz, CH2), 2.00 (d, 1H, J =16.0 Hz, CH2), 1.02 (s, 3H, CH3), 0.90 (s, 3H, CH3). ^{13}C NMR (75 MHz, DMSO-d_6): 27.1, 29.2, 32.5, 38.0, 50.4, 57.8, 108.19, 121.6, 124.0, 128.5, 146.3, 150.8, 150.9, 158.1, 194.4; ESI-MS(m/z): 339.2 $[M+H]^+$

2-Amino-4-(4-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo1,4,5,6,7,8-hexahydroquinoline (5e)

IR(KBr cm^{-1}): 3425, 3327, 3265, 2965, 2175, 1655, 1475, 1365, 675; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.95-2.90 (dd, 2H, J=15 Hz, CH_2), 2.73-2.95 (dd, 2H, J=17.0, CH_2), 4.80 (s, 1H, CH), 5.90 (s, 2H, NH_2), 6.60-7.00, (m , 4H Ar-H), 7.20-8.55, (br, s 1HNH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.5, 31.5, 39.5, 43.5, 52.7, 59.5, 111.5, 115.3, 115.5, 135.3, 139.2, 156.5, 162.0, 199.5; ESI-MS(m/z): 372 $[M+H]^+$

Table 3: Synthesis of hexahydroquinoline derivatives by using MSA catalyst under MWI.

Entry	R	Time in Min.	Yield %	Melting Point ºC	
				Obtained	Reported [Ref]
5a	-H	6	91	272-274	275-277 [25]
5b	-4-OCH3	4	96	290-292	288-289 [26]
5c	-4-Cl	5	93	288-290	290-291 [26]
5d	3-NO_2	5	92	281-282	282-283 [26]
5e	-4-Br	6	91	291-293	295-296 [25]
5f	-4-CH3	5	92	295-297	294-295 [27]
5g	-4-OH	6	90	290-292	293-295 [25]
5h	-2-Br	7	89	283-285	285-287 [25]
5i	-2-Cl	7	87	270-272	273-276 [25]
5j	-2-F	4	82	297-299	299-300 [27]

[a]Reaction conditions: Benzaldehyde (0.01 mol), dimedone (0.01 mol), malononitrile (0.01 mol), and ammonium acetate (0.02 mol), catalyst (6 mol%) & ethanol 10 mL. [b]Isolated yields. [b]Isolated yields.

2-Amino-4-(4-methylphenyl)-3-cyano-7,7-dimethyl-5-oxo1,4,5,6,7,8-hexahydroquinoline (5f)
IR(KBr cm^{-1}): 3392, 3313, 3245, 2922, 2176, 1671, 1610, 1485.; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.93(s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.96-2.19 (dd, 2H, J=15 Hz, CH2), 2.34- 2.45 (dd, 2H, J=17.2, CH2), 4.44 (s, 1H, CH), 5.95 (s, 2H, NH_2), 6.90-7.32 (dd , 2H Ar-H), 6.92-7.01, (dd , 2H Ar-H), 7.16-8.4, (br, s 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 28.0, 29.5, 32.5, 43.1, 55.4, 59.0, 112.2, 122.9, 123.9, 128.2, 128.4, 131.4, 146.5, 151.0, 163.2, 197.0; ESI-MS(m/z): 307 $[M+H]^+$

2-Amino-4-(4-hydroxyphenyl)-3-cyano-7,7-dimethyl-5-oxo1,4,5,6,7,8-hexahydroquinoline (5g)
IR(KBr cm^{-1}): 3427, 3317, 3176, 2975, 2684, 1674, 1495, 1381.; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.93(s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.91-2.85 (dd, 2H, J=15 Hz, CH_2), 2.70- 2.90 (dd, 2H, J=17.0, CH_2), 4.40 (s, 1H, CH), 5.95 (s, 2H, NH_2), 6.65-7.00, (dd , 2H Ar-H), 6.60-7.05, (dd , 2H, Ar-H), 7.15-8.3, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.6, 32.4,38.2, 43.5,51.3, 57.1, 111.8,115.5,115.6, 134.9, 135.2, 155.5, 163.0, 198.4; ESI-MS(m/z): 309.3 $[M+H]^+$

2-Amino-4-(2-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo1,4,5,6,7,8-hexahydroquinoline (5h)
IR(KBr cm^{-1}): 3455, 3341, 3162, 2945, 2675, 1651, 1422, 1383, 755; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.95-2.90 (dd, 2H, J=15 Hz, CH_2), 2.75-2.95 (dd, 2H, J=17.0, CH2), 4.66 (s, 1H, CH), 5.96 (s, 2H, NH_2), 6.60-7.50, (m , 4H, Ar-H), 7.16-8.55, (br, s 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.4, 31.2, 39.4, 43.5, 52.7, 59.6, 111.8, 114.3, 113.5, 130.4, 135.7, 150.3, 163.0, 197.4; ESI-MS(m/z): 372 $[M+H]^+$

2-Amino-4-(2-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo1,4,5,6,7,8-hexahydroquinoline (5i)
IR(KBr cm^{-1}): 3440, 3335, 3135, 2925, 2665, 1695, 1445, 1385,725.; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.15 (s, 3H CH_3), 1.95-2.90 (dd, 2H, J=15 Hz, CH_2), 2.75-2.95 (dd, 2H, J=17.0, CH_2), 4.60 (s, 1H, CH), 5.95 (s, 2H, NH_2), 6.65-7.00, (m, 4H, Ar-H), 7.15-8.9, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.3, 31.5, 39.5, 43.5, 51.5, 57.5, 112.5, 116.4, 118.7, 131.9, 135.2, 155.5, 163.0, 195.4; ESI-MS(m/z): 327.8 $[M+H]^+$

2-Amino-4-(2-fluorophenyl)-3-cyano-7,7-dimethyl-5-oxo1,4,5,6,7,8-hexahydroquinoline (5j)
IR(KBr cm^{-1}): 3489, 3345, 3128, 2972, 2685, 1685, 1493, 1391,745; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.96 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.92-2.95 (dd, 2H, J=15 Hz, CH_2), 2.75-2.90 (dd, 2H, J=17.0, CH_2), 4.51 (s, 1H, CH), 5.85 (s, 2H, NH_2), 6.65-7.05, (m , 4H, Ar-H), 7.17-8.5, (br, s 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.4, 32.5, 38.1, 43.2, 51.5, 57.5, 111.5, 115.4, 117.7, 130.8, 135.2, 153.5, 165.0, 196.4; ESI-MS(m/z): 311.3 $[M+H]^+$

IV. CONCLUSION

We have developed a novel, one-pot, four component reaction under microwave irradiation that offers a simple, efficient and environmentally benign route for the synthesis of hexahydroquinolines and its

derivatives exhibiting biological importance in good to excellent yields. Methane sulfonic acid showed high catalytic activity in the synthesis of hexahydroquinolines. Our new method offers several obvious advantages including short reaction times, the use of mild reaction conditions, avoiding of discharging harmful organic solvents and acids and involving a simple work-up procedure.

ACKNOWLEDGEMENT

Authors are thankful to the Principal, Indraraj Arts, Commerce and Science College, Sillod, Chhatrapati Sambhajinagar, Maharashtra, India for his encouragement and support during this endeavour. We also extend our thanks to the Principal Deogiri College, Chhatrapati Sambhajinagar, Maharashtra, India for providing laboratory facilities to carry out this research work.

REFERENCE

[1] D. Patil, D. Chandam, A. Mulik, S. Jagdale, P. Patil, & M. Deshmukh, One pot four component sequential synthesis of hexahydroquinoline derivatives in aqueous media via enaminone intermediates: A green protocol, *J. of Saudi Chem. Soc.*, vol. 21, pp. S329–S338, 2014.

[2] A. Sapkal, S. Sapkal, & and B. Madje, Microwave-assisted ionic liquid catalyzed one-pot synthesis of hexahydroquinoline derivatives, *Eur. Chem. Bull*., vol. 8 (11), pp. 352-355, 2019.

[3] E. Heny, A. Indwiani, & A. Mustafa, Anticancer Activity of Calanone on He-La Cell Line, *Indones J. Chem*., vol. 10, pp. 240-244, 2010.

[4] A. E. Fazary, Metal complexes of salicylhydroxamic acid and 1,10-phenanthroline: equilibrium and antimicrobial activity studies, *Bull. Chem. Soc. Ethiop*., vol. 28 (3), pp. 393-402, 2014.

[5] A. J. Johnson, R. A. Kumar, S. A. Easheed, S. P. Chandrika, A. Chandrasekhar, S. Baby, & A. Subramoniam, Antipyretic, analgesic, anti-inflammatory, and antioxidant activities of two significant chromenes from Melicope luna-ankenda., *J. Ehanopharmacology*., vol. 130 (2), 267-271, 2010.

[6] R. N. Krishna, M. S. Surendrababu, M. V. Basaveswararao, & T. Nageswararao, A Novel Synthesis and Characterization of 1,2,3,4-Tetrahydropyrimidine-2(1H)-thiones, *Asian. J. Chem*., vol. 29 (4), pp. 882-884, 2017.

[7] H. Nishino, T. Okuyama, M. Takata, S. Shibita, H. Tokuda, & J. Takayasu, Studies on the anti-tumor-promoting activity of naturally occurring substances. IV. Pd-II [(+) anomalin, (+) praeruptorin B], a seselin-type coumarin, inhibits the promotion of skin tumor formation by 12-Otetradecanoylphorbol-13-acetate in 7,12-dimethylbenz[a]anthracene-initiated mice *Carcinogenesis*, vol. 11 (9), pp. 1557-1561, 1990.

[8] M. S. Al-Said, M. M. Ghorab, M. S. Al-Dosari, & M. M. Hamed, Synthesis and in vitro anticancer evaluation of some novel hexahydroquinoline derivatives having a benzenesulfonamide moiety, *Eur J Med Chem.*, vol. 46 (1), pp. 201-207, 2011.

[9] D. L. Simmons, R. M. Botting, & T. Hla, Cyclooxygenase Isozymes: The Biology of Prostaglandin Synthesis and Inhibition, *Pharmacol Rev*. vol. 56 (3), pp. 387-437, 2004.

[10] S. Dey, P. Basak, & P. Ghosh, A Green Synthetic Approach Towards One Pot Multi Component Synthesis of Hexahydroquinoline and 9-Arylhexahydroacridine-1,8-dione Derivatives Catalyzed by Sulphonated Rice Husk.; *Euro. J. Chem. Soc.*, vol. 5, pp. 15209 – 15217, 2020.

[11] M. Abdollahi-Alibeik, & A. Rezaeipoor-Anari, Fe_3O_4@B-MCM-41*:* A new magnetically recoverable nanostructured catalyst for the synthesis of polyhydroquinolines, *J. of Magnetism and Magnetic Materials,* vol. 398, pp. 205–214, 2016.

[12] G. Sabitha, G. S. K. K. Reddy, C. S. Reddy, & J. S. Yadav, A novel TMSI-mediated synthesis of Hantzsch 1,4-dihydropyridines at ambient temperature, *Tetrahedron Letters*, vol. 44 (21), pp. 4129–4131, 2003.

[13] D. Azarifar, Y. Abbasi, & O. Badalkhani, N-(3-silyl propyl) diethylene triamine N, N', N''-tri-sulfonic acid immobilized on Fe_3-xTiO_4 magnetic nanoparticles: A new recyclable heterogeneous nanocatalyst for the synthesis of hexahydroquinolines. *Appl. Organomet. Chem.*, vol. 32 (1), pp. 3939, 2017.

[14] M. S. Sheik, K. Aswin, K. Logaiya, & S. P. N. Sudhan, Bismuth nitrate as an efficient recyclable catalyst for the one-pot multi component synthesis of 1,4-dihydropyridine derivatives

through unsymmetrical Hantzsch reaction, *J. of Saudi Chem. Soc.*, vol. 20, pp. S100–S108, 2016.

[15] N. Sahiba, A. Sethiya, J. Soni, & S. Agarwal, Acridine-1,8-diones: Synthesis and Biological Applications, *Chemistry Select*, vol. 6 (9), pp. 2210–2251, 2021.

[16] H. T. Nguyen, V. A. Truong, & P. H. Tran, Synthesis of polyhydroquinolines and propargylamines through one-pot multicomponent reactions using an acidic ionic liquid immobilized onto magnetic Fe_3O_4 as an efficient heterogeneous catalyst under solvent-free sonication, *RSC Advances*, vol. 10 (42), pp. 25358–25363, 2020.

[17] K. S. Kumar, A. R. Robert, N. Kerru, & S. Maddila, A novel, swift, and effective green synthesis of morpholino-pyridine analogues in microwave irradiation conditions, *Results in Chem.*, C:\Users\archana\Downloads\Volume 5vol. 5, pp. 100692, 2023.

[18] A. Davoodnia, M. Khashi, & N. Tavakoli-Hoseini, Tetrabutylammonium hexatungstate [TBA]2[W6O19]: Novel and reusable heterogeneous catalyst for rapid solvent-free synthesis of polyhydroquinoline via unsymmetrical Hantzsch reaction, *Chin. J. of Catalysis*, vol. 34 (6), pp. 1173–1178, 2013.

[19] S. Tabassum, S. Govindaraju, R. R. Khan, & M. A. Pasha, Ultrasound mediated, iodine catalyzed green synthesis of novel 2-amino-3-cyano-4H-pyran derivatives, *Ultrasonics Sonochemistry, vol.* 24, pp. 1–7, 2015.

[20] L. M. Wang, J. Sheng, L. Zhang, J. W. Han, Z. Y. Fan, H. Tian, & C. T. Qian, Facile Yb $(OTf)_3$ promoted one-pot synthesis of polyhydroquinoline derivatives through Hantzsch reaction, *Tetrahedron*, vol. 61 (6), pp. 1539–1543, 2004.

[21] L. S. Gadekar, S. S. Katkar, S. R. Mane, B. R. Arbad, and M. K. Lande, Scolecite Catalyzed Facile and Efficient Synthesis of Polyhydroquinoline Derivatives through Hantzsch Multi-component Condensation, *Bull. Korean Chem. Soc*.vol. 30 (11), pp. 2532-2534, 2009.

[22] C. S. Reddy, & M. Raghu, Cerium (IV) ammonium nitrate catalysed facile and efficient synthesis of polyhydroquinoline derivatives through Hantzsch multicomponent condensation. *Chin. Chem. Let*., vol. 19 (7), pp. 775–779, 2008.

[23] J. L. Donelson, R. A. Gibbs, & S. K. De, An efficient one-pot synthesis of polyhydroquinoline derivatives through the Hantzsch four component condensation, *J. of Mol. Catalysis*, vol. 256 (1-2), pp. 309–311, 2006.

[24] P. Kulkarni, Methane Sulphonic Acid is Green Catalyst in Organic Synthesis, *Orien. J. of Chem.*, vol. 31 (1), pp. 447–451, 2015.

[25] T. Shujiang, J. Zhang, X. Zhu, Y. Zhang, Q. Wang, X. Jianing, B. Jiang, R. Jia, J. Zhang, & F. Shi, One-pot synthesis of hexahydroquinolines via a four-component cyclocondensation under microwave irradiation in solventfree conditions: A green chemistry strategy., *J. Heterocyclic Chem*., vol. 43 (4), pp. 985-988, 2006.

[26] S. Tu, J. Zhang, X. Zhu, Y. Zhang, Q. Wang, J. Xu, & F. Shi, One-pot synthesis of hexahydroquinolines Via four-component cyclocondensation under microwave irradiation in solvent free conditions: A green chemistry strategy, *J. of Hetero. Chem.*, vol. 43 (4), pp. 985–988, 2006.

[27] S. Kumar, P. Sharma, K. K. Kapoor, & M. S. Hunda, An efficient, catalyst- and solvent-free, four-component, and one-pot synthesis of polyhydroquinolines on grinding. *Tetrahedron*., vol. 64 (3), pp. 536-542, 2008.