

[Emim]OH ionic liquid catalyzed efficient synthesis of Polyhydroquinolines derivatives via Hantzsch reaction as green approach

Devidas S. Bhagat¹, Maya V. Katariya², Akshay D. Takwale², Anil D. Bhadke² and Rajendra P. Pawar^{2*}, Pravin S. Kendrekar³

¹Department of Forensic Chemistry, Government Institute of Forensic Science, Aurangabad. 431001 MS, India

²Department of Chemistry, Deogiri College, Station Road, Aurangabad 431 005, MS, India.

³Department of Chemistry and Directorate: Research Development, University of the Free State, Nelson Mandela Drive 205, Bloemfontein 9301, South Africa.

*corresponding author: rppawar@yahoo.com

Received: 18-5-2016

Revised: 19-6-2016

Published: 23-6-2016

Keywords:

[Emim]OH,
Polyhydroquinolines,
Hantzsch reaction, Multi
component reaction (MCRs),
Green chemistry

Abstract: Ionic liquid [Emim]OH is reported an efficient catalyst for one pot multi component synthesis of Polyhydroquinolines via the Hantzsch reaction. The mild reaction conditions, short reaction times, high yields and the remarkably low toxicity of ionic liquid makes this methodology greener and efficient

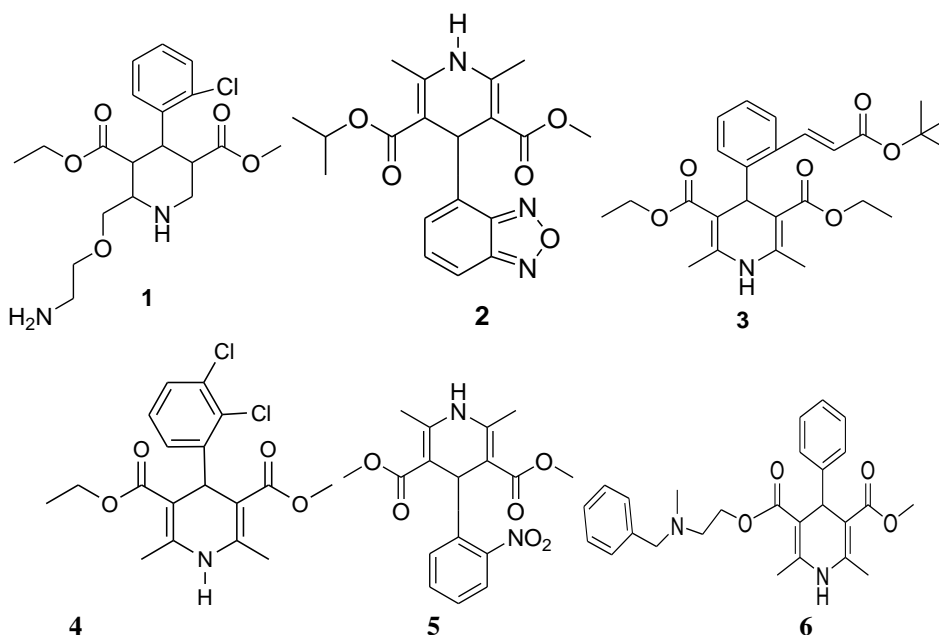
Cite this article as: Bhagat, D.S., Katariya, M.V., Takwale, A.D., Bhadke, A.D. and Pawar, R.P. (2016) [Emim]OH ionic liquid catalyzed efficient synthesis of Polyhydroquinolines derivatives via Hantzsch reaction as green approach. *Journal of basic and applied Research* 2(4): 448-454
Like us on Facebook - [CLICK HERE](#) Join us on academia - [CLICK HERE](#) Be co-author with JBAAR on Google Scholar - [CLICK HERE](#)

INTRODUCTION:

Multi component reactions (MCRs) is an efficient and powerful tool in modern organic chemistry for the synthesis of biologically active and complex potent molecules from readily available substrates without isolation of intermediates in shorter reaction time with maximum selectivity with high atom economy and high purity with good yields.

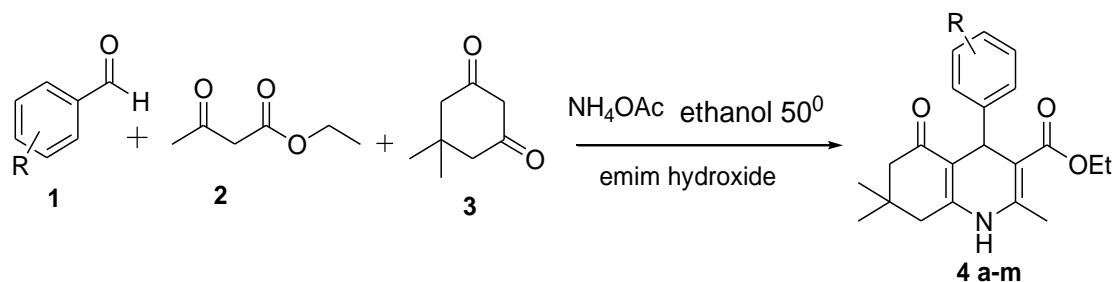
Amlodipine¹, isradipine², lacidipine³, felodipine⁴, nifedipine⁵ and nicardipine⁶ are the prominent drugs used in the treatment of different diseases like effective calcium channel blockers in cardiovascular diseases (Songab, G. and Wang, B. et.al.2005), 1,4-Dihydropyridines possess a variety of biological activities (Sapkal, S. and Shelke, K. et.al.2009), such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective,

hepatoprotective, and antidiabetic agents (Khojastehnezhad, A. and Moeinpour, F. et.al.2011), antimalarial, antiinflammatory, antiasthmatic, antibacterial, and tyrosine kinase inhibiting agents (Kumar, S. and Sharma, P. et.al.2008), platelet antiaggregatory activity (Baghbanian, S. and Khaksar, S. et.al.2010), calcium channel agonist-antagonist modulation activities (Shan, R., and Velazquez, C., et.al. 2004), cerebral antischemic activity in the treatment of Alzheimer's disease (Zonouz, A. and Moghani D. et.al. 2010), chemosensitizers (Hong, M. and Cai, C. et.al. 2010), polyhydroquinoline compounds not only attracted the attention of chemists for synthesis but also creating an interest of research challenge.



Some representative examples of catalysts used for synthesis of derivatives of polyhydroquinolines include as iodine(Wang, X. and Yang, K. et.al. 2010), metal triflates(Ko, S. and Sastry, M., et.al. 2005), L-proline(Kumar, A. &Maurya, R. 2007), FeF₃(Surasani, R., and Kalita, D. et.al. 2012), CAN(Ko, S. and Yao, C., 2006), Bismuth(III) bromide(Yoo, J. and Laughlin, T., 2015), 2-Methylpyridinium Trifluoromethanesulfonate (Tajbakhsh, M. and Alinezhad, H. et.al. 2013), P(4-VPH)HSO₄ (Janardhan, B., and Rajitha, B. et.al.2014), Scandium triflate(Donelson, J. and Gibbs, R. et.al 2006), Gd(OTf)₃(Mansoor, S. and Aswin, K., 2012), Hafnium (IV) bis(perfluorooctanesulfonyl)imide complex (Hong,

M. and Cai, C. et.al.2010) etc. Development of green process is the need of society (Gollapalli Naga Raju, et.al.2016). Ionic liquids (ILs) as a new class of catalysts or solvents, have attracted growing research interest recently because of their versatile properties like nonflammable, negligible vapor pressure, wide liquid range and high thermal stability (Ren, Y. and Jin, S., 2015), IL supposed as novel chemical agents and widely regarded as a greener solvent in many organic transformation because they are designable, recyclable and non-volatile properties (Troncoso, J., Cerdeiriña, C. et.al.2006).



Scheme-1

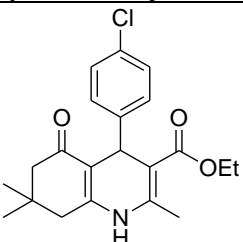
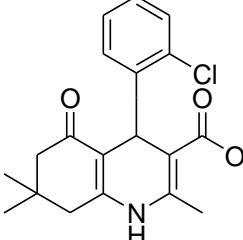
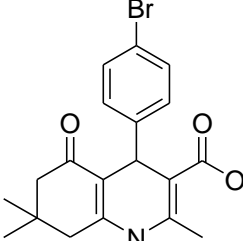
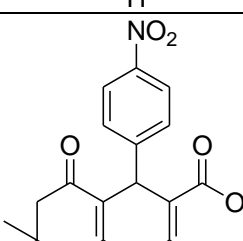
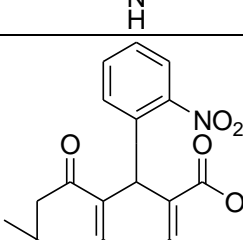
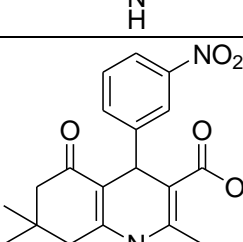
Table.1 Screening of solvent

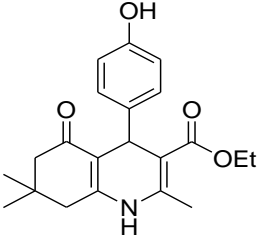
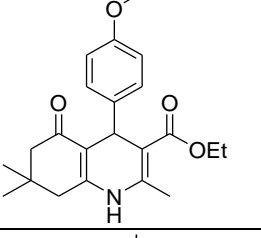
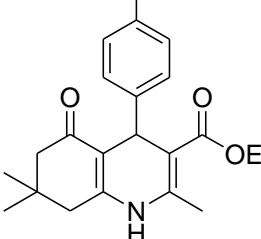
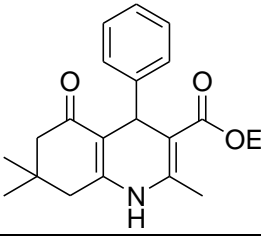
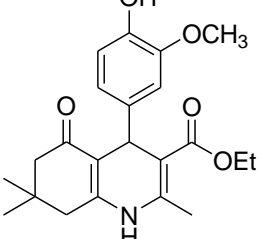
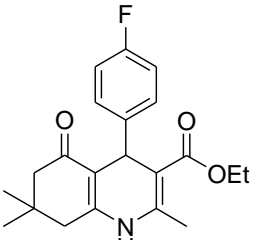
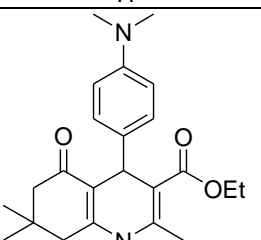
Sr. No.	Catalysts	Time (hrs/min)	Yield (%)	Temp. (°C)	Solvent	Ref. No.
1	L-proline	1-3hr	73	60	Ethanol	Kumar, A. &Maurya, R. 2007
2	FeF ₃	12hr	92	80 ⁰	Ethanol	Surasani, R. and Kalita, D. et.al. 2012
3	CAN	1hr	70-84	RT	Ethanol	Ko, S. and Yao, C., 2006
4	Bismuth(III) bromide	2hr	86	RT	Ethanol	Yoo, J. and Laughlin, T., 2015
5	[2-MPyH]OTf	2hours	60-75	RT	H2O	Tajbakhsh, M. and Alinezhad, H. et.al. 2013
6	P(4-VPH)HSO ₄	20minutes	94	reflux	H2O	Janardhan, B. and Rajitha, B. et.al.2014
7	Scandium triflate	4hr	93	RT	Ethanol	Donelson, J. and Gibbs, R. et.al 2006
8	Gd(OTf) ₃	5hr	89	RT	Ethanol	Mansoor, S. and Aswin, K., 2012
7	[Emim]OH	1hr	90-95	50 ⁰	Ethanol	Present work
8.	B-CD-SO ₃ H	1.5hr	80-90	50 ⁰	ethanol	Present work

Table2. Catalyst concentration evaluation

Sr.No.	Catalyst (ml)	Temperature(°C)	yield	Time(Hour)
1.	00	RT	Trace	1
2.	00	50	20	1
3.	0.1	RT	35	1
4.	0.1	50	42	1
5.	0.2	RT	40	1
6.	0.2	50	48	1
7.	0.3	RT	42	1
8.	0.3	50	55	1
9.	0.4	RT	51	1
10.	0.4	50	72	1
11.	0.5	RT	60	1
12.	0.5	50	90-95	1
13.	0.6	RT	61	1
14.	0.6	50	90-95	1

Table.3 Synthesized of Polyhydroquinolines derivatives

Entry	Synthesized compound	Time (minutes)	Yield ^a	Melting point °C
a		50	95	241-243
b		55	92	208-210
c		50	93	252-255
d		45	95	245-248
e		1 hr	89	207-210
f		50	92	180-183

g		1hr	88	234-236
h		1hr	90	255-257
i		55	91	258-260
j		55	90	202-205
k		1 hr	87	231-233
l		50	95	184-186
m		1 hr	91	256-259
Reaction conditions: Aldehyde1(1 mmol), ethyl acetoacetate 2(1 mmol), dimedone3 (1 mmol), and ammonium acetate (1.5 mmol) in ethanol (5.0 mL) was added [Emim]OH (0.5mL) ^a :Isolated yield				

MATERIALS AND METHODS

Chemicals were purchased from Spectrochem and Sigma aldrichchemical companies in high purity, used without further purification. All the materials were of commercial grade reagent. Melting points of synthesized derivatives were determined in open capillaries visual melting point apparatus . Infrared (IR) spectra in KBr were recorded using a Perkin-Elmer FT-IR spectrometer 65. ^1H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in CDCl_3 as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. The progresses of the reactions were monitored by TLC (Thin Layer Chromatography).

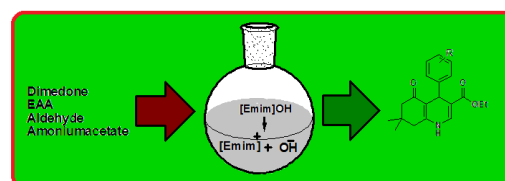
RESULT AND DISCUSSION

In demonstration of the best experimental reaction conditions for the reaction of aldehyde (1.1 mmol) 1, Ethyl acetoacetate(1.1 mmol) 2, dimedone(1.1 mmol)3 and amoniun acetate(1.5mmol) in the presence of catalytic amount [Emim]OH (0.5ml) in 5ml ethanol was considered as a standard model reaction (Scheme 1). For optimizing the various reaction parameters the reaction between of p-chloroaldehyde, ethylacetoacetate(1mmol), dimedone(1mmol) and amoniunacetate(1.5mmol) was chosen as a model reaction Initially, the reaction was optimized by varying concentration of ionic liquid in ml (Table 2). The reaction shows good results in terms of yield and rate of reaction with 0.5 ml of ionic liquid stirred at 50° (entry 12table no. 2). Further increase in concentration of ionic liquid did not affect the time or yield of the reaction. For complete conversion it takes 45 minute to one hour at 50° temperature on constant stirring. The ionic liquid shows moderate yield at room temperature as compared to reaction mixture

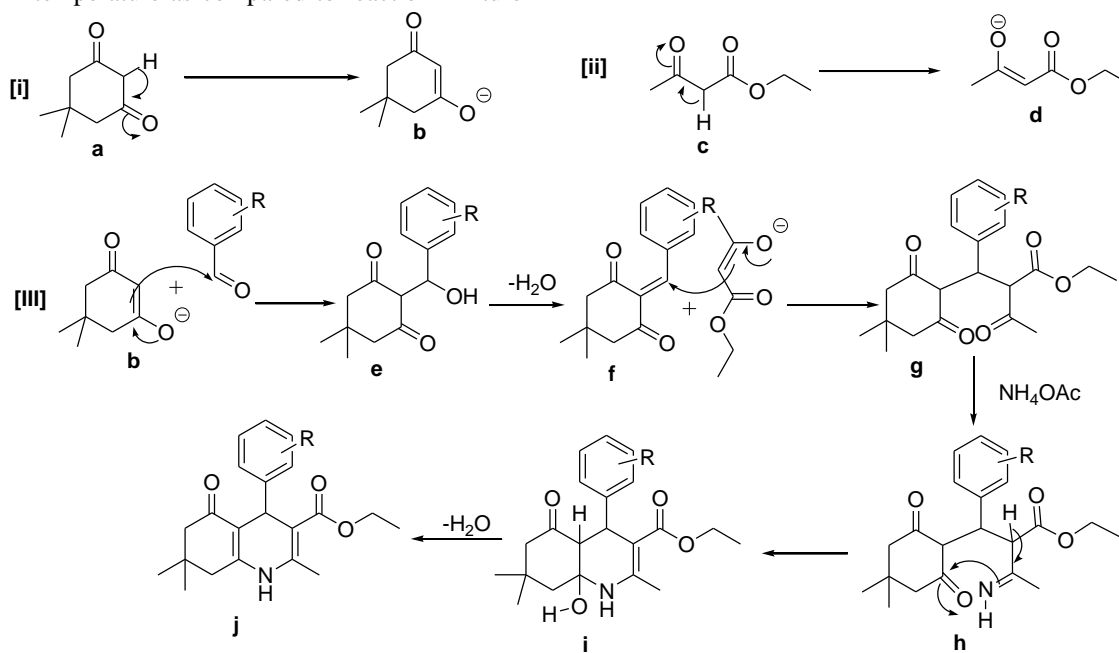
stirred at 50° , this condensation gives good yield of 0.5ml catalytic concentration of ionic liquid at 50° (Table.2). Further increase the catalyst concentration and temperature does not affect the yield and reaction time of completion. In (Table-1, Entry 8) compared the catalytic activity of sulphonatedbetacyclodextrin ($\beta\text{-CD-SO}_3\text{H}$) and ionic liquid required less time for completion, but $\beta\text{-CD-SO}_3\text{H}$ is also good catalyst for this transformation. IR spectrum exhibited sharp bands at $3200\text{-}3300(\text{NH})$, $1700\text{-}1730\text{ cm}^{-1}(>\text{C}=\text{O})$, $3100\text{-}3300\text{ cm}^{-1}(\text{N-H})$ illustrates the formation of products.

REACTIONMECHANISM

The [EMIM]OH acts as a base in this reaction mechanism. In presence of this catalyst dimedone undergoes enolisation a to b and also ethyl acetoacetate (EAA) undergoes enolisation from c to d. The b and aromatic aldehyde on condensation give intermediate e. The intermediate e on $\text{E}_{1\text{c}}\text{b}$ elimination gives intermediate f. The intermediate f and d on Michael addition gave intermediate g. The intermediate g reacts with ammonium acetate to give intermediate h. The intermediate h on intramolecular cyclisation gives intermediate i. The intermediate i on $\text{E}_{1\text{c}}\text{b}$ elimination gives Polyhydroquinolines j.



PLAUSIBLE REACTION MECHANISM



General procedure for Synthesis of ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenylquinoline-3-carboxylate:

To a mixture aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate(1.5 mmol) in ethanol (5.0 mL) was added [Emim]OH (0.5mL). The reaction vessel was stirred at 50⁰ for 1 hour. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was cooled to room temperature and then poured onto ice cold water. The obtained product was recrystallized in ethanol. Some derivatives were purified by column chromatography technique. The structures of synthesized compounds were confirmed by comparison of their melting points with authentic values reported in literature and spectral techniques ¹H NMR, IR, and LRMS. The spectral data of representative compounds are described below

Spectral data for representative derivative Polyhydroquinolines:

Ethyl 1,4,5,6,7,8-hexahydro-4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate

Yellow solid; yield 88%; mp234-236°C; recrystallised in ethanol; IR (KBr) 3279, 3205, 1681, 1492, 1380, 1218 cm⁻¹; H¹ NMR (CDCl₃) 0.8-1.0 (s, 6H), 1.20 (s, 3H), 1.9-2.2 (m, 7H)4.00 (q, 2H), 4.1 (s, 1H), 4.8 (s, 1H), 6.7 (d, 2H), 6.9 (d, 2H), 9.0 (d, 1H), LRMS m/z(M+39)⁺394.

Ethyl 4-(4-bromophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate

Yellow solid; yield 93%; mp252-255°C; recrystallised in ethanol; IR (KBr) 3273, 3203, 3078, 1704, 1699,cm⁻¹; H¹ NMR (CDCl₃) 0.8-0.9 (s, 6H), 1.20 (s, 3H), 1.8-2.3 (m, 7H), 4.00 (q, 2H), 4.8 (s, 1H), 7.1 (d, 2H), 7.3 (d, 2H), 9.0 (d, 1H), LRMS m/z(M⁺)423, 407, 385.

CONCLUSION:

In present work, we have demonstrated the utility of the combination of catalytic amount of [Emim]OH in ethanol for the synthesis of ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenylquinoline-3-carboxylate from aromatic aldehydes, dimedone, malononitrile and ammonium acetate at room temperature. The presence of basic ionic liquid (IL) in catalytic amount in ethanol are good combination for synthesis. This method gives the products in minimum time with excellent yields, involving simple workup procedure and does not harm the environment. Mild and efficient method for the multicomponent synthesis using a relatively nontoxic and noncorrosive ionic liquid catalyst is reported

ACKNOWLEDGMENT:

We are thankful to the Department of Chemistry, Deogiri College, Aurangabad, India for providing laboratory facilities and the permission to use facility the Central Research Laboratories and Council of Scientific and Industrial Research (CSIR), New Delhi (110 012) for financial support under Senior Research Fellowship.

REFEERENCE

- Songab, G., Wanga, B., Wu, X., Kang, Y. &Yang,L., (2005), Montmorillonite K10 Clay: An Effective Solid Catalyst for One-Pot Synthesis of Polyhydroquinoline Derivatives, 35(22), 2875-2880. DOI:10.1080/00397910500297255
- Sapkal, S., Shelke, K., Shingate, B. &Shingare, M. (2009), Nickel nanoparticle-catalyzed facile and efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation under solvent-free conditions, *Tetrahedron Lett.*,50(15), 1754-1756. doi:10.1016/j.tetlet.2009.01.140
- Khojastehnezhad, A., Moeinpour, F. &Davoodnia A., (2011), PPA-SiO₂ catalyzed efficient synthesis of polyhydroquinoline derivatives through Hantzsch multicomponent condensation under solvent-free conditions, *Chin. Chem. Lett.*22(7), 807-810. doi:10.1016/j.ccllet.2010.12.051
- Kumar, S., Sharma, P., Kapoor , K. &Hundal, M., (2008) An efficient, catalyst- and solvent-free, four-component, and one-pot synthesis of polyhydroquinolines on grinding; *Tetrahedron*, 64(3), 536-542, doi:10.1016/j.tet.2007.11.008
- Baghbanian, S., Khaksar, S., Vahdat, S., Farhang, M. &Tajbakhsh,M., (2010), One-step, synthesis of Hantzschesters and polyhydroquinoline derivatives using new organocatalyst, 21(5), 563-567. doi:10.1016/j.ccllet.2009.12.011
- Shan, R., Velazquez, C. &Knaus, E., (2004), Syntheses, calcium channel agonist-antagonist modulation activities, and nitric oxide release studies of nitrooxyalkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2,1,3-benzoxadiazol-4-yl)pyridine-5-carboxylate racemates, enantiomers, and diastereomers, *J. Med. Chem.* 47(1), 254,261, doi10.1021/jm030333h.
- Zonouz ,A. &Moghani D., (2010), Synthesis of 1,4-Dihydropyridine Derivatives Under Solvent-Free and Grinding Conditions, *syn. Comm.* 41(41), 2152-2160. doi:10.1080/00397911.2010.499488
- Lingaiah, N., Satyender, A., Subhashini, G., Rajashaker, B., Venu C. M. & Srinivas, K., (2008), A Facile Synthesis of Polyhydroquinoline Derivatives via the Hantzsch Reaction Under Solvent Free-

- Conditions Using Potassium Dodecatungstocobaltate Trihydrate ($K_5CoW_{12}O_{40}.3H_2O$), *Int. Org. Chem.*, 5(1), 60-64.
doi: <http://dx.doi.org/10.2174/157017808783330162>
- Wang, X., Yang, K., Zhou, J. & Shu-Jiang Tu, (2010), Facile Method for the Combinatorial Synthesis of 2,2-Disubstituted Quinazolin-4(1H)-one Derivatives Catalyzed by Iodine in Ionic Liquids, *J. Comb. Chem.*, 2(4), 417-421, doi: 10.1021/cc900174p
- Ko, S., Sastry, M., Lin, C. & Yao, C., (2005), Molecular iodine-catalyzed one-pot synthesis of 4-substituted 1,4-dihydropyridine derivatives via Hantzsch reaction. *Tetrahedron Lett.*, 46(34), 5771-5774, doi:10.1016/j.tetlet.2005.05.148
- Kumar, A. & Maurya, R. (2007), Synthesis of polyhydroquinoline derivatives through unsymmetric Hantzsch reaction using organocatalysts, *Tetrahedron*, 63(9), 1946-1952. doi:10.1016/j.tet.2006.12.074
- Surasani, R., Kalita, D., Rao, A. V. D., Yarbaji, K. & Chandrasekhar, K. B., (2012), FeF₃ as a novel catalyst for the synthesis of polyhydroquinoline derivatives via unsymmetrical Hantzsch reaction, *J. Fluorine Chem.*, 135(1), 91-96. doi:10.1016/S0022-1139(12)00032-2
- Ko, S. & Yao, C., (2006), Ceric Ammonium Nitrate (CAN) catalyzes the one-pot synthesis of polyhydroquinoline via the Hantzsch reaction; *Tetrahedron*, 62(31), 7293-7299. doi:10.1016/j.tet.2006.05.037
- Yoo, J., Laughlin, T., Krob, J. & Mohan, R., (2015) Bismuth(III) bromide catalyzed synthesis of polyhydroquinoline derivatives via the Hantzsch reaction; *Tetrahedron Letters*, 56(27), 4060-4062, doi:10.1016/j.tetlet.2015.04.121
- Tajbakhsh, M., Alinezhad, H., Norouzi, M., Baghery, S. & Akbari, M., (2013), Proticpyridinium ionic liquid as a green and highly efficient catalyst for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation in water, *Journal of Molecular Liquids*, 177, 44-48. doi:10.1016/j.molliq.2012.09.017
- Janardhan, B., Rajitha, B. & Crooks, P., (2014), Poly(4-vinylpyridinium)hydrogen sulfate: An efficient heterogeneous catalyst for the one-pot synthesis of polyhydroquinolines via unsymmetrical Hantzsch reaction in aqueous medium, *Journal of Saudi Chemical Society*, 18(5), 722-727. doi:10.1016/j.jscs.2014.01.009
- Donelson, J., Gibbs, R. & De, S. (2006), An efficient one-pot synthesis of polyhydroquinoline derivatives through the Hantzsch four component condensation, *J. Mol. Catal. Chem.* 256(1) 309-311, doi:10.1016/j.molcata.2006.03.079
- Mansoor, S., Aswin, K., Logaiya, K. & Sudhan, S. (2012) An efficient one-pot multi component synthesis of polyhydroquinoline derivatives through Hantzsch reaction catalysed by Gadolinium triflate; *Arabian Journal of Chemistry*, doi:10.1016/j.arabj.2012.10.017
- Hong, M., Cai, C. & Yi, Wen-Bin (2010), Hafnium (IV) bis(perfluorooctanesulfonyl)imide complex catalyzed synthesis of polyhydroquinoline derivatives via unsymmetrical Hantzsch reaction in fluorosulfuric acid medium *J. Fluorine Chem.*, 131(1), 111-114. doi:10.1016/j.jfluchem.2009.10.009
- Gollapalli Naga Raju, Karumudi Bhavya Sai, Kondeti T Naveen, Rama Rao Nadendla, (2016), Green Synthesis & Biological Evaluation of Novel Benzimidazole Derivatives as Antianxiety Agents, *J. basic appl. Res*; 2(3), 221-225. Doi:..
- Ren, Y., Jin, S., Yan, H. & Zhang, Ze., (2014), PEG1000-Based Dicationic Acidic Ionic Liquid Catalyzed One-Pot Synthesis of 4-Aryl-3-Methyl-1-Phenyl-1H-Benzo[h]pyrazolo [3,4-b]quinoline-5,10-Diones via Multicomponent Reactions; *Catalysts*, 4(6), 1649-1656. doi:10.1080/00304948.2014.963455.
- Troncoso, J., Cerdeiriña, C., Sanmamed, Y., Romani, L., Paulo, L. & Rebelo, N., (2006) Thermodynamic Properties of Imidazolium-Based Ionic Liquids: Densities, Heat Capacities, and Enthalpies of Fusion of [bmim][PF₆] and [bmim][NTf₂], *J. Chem. Eng. Data*, 51 (5), 1856-1859. doi:10.1021/je060222y.