A catalyst free, one pot approach for the synthesis of quinoxaline derivatives via oxidative cyclisation of 1,2-diamines and phenacyl bromides

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Graphical Abstract

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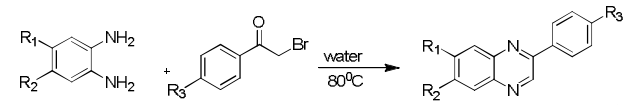

$R_1 = R_2 = H, CH_3$
$R_1 = H, R_2 = Cl, Br, CH_3$

$R_3 = H, Cl, Br, OCH_3, CH_3$

25 examples
Yield upto 85%

no catalyst
no additive
no acid or base
no surf actant
no nanoparticles
no oxidant

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A catalyst free, one pot approach for the synthesis of quinoxaline derivatives *via* oxidative cyclisation of 1,2-diamines and phenacyl bromides

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ABSTRACT

A simple, efficient and eco-friendly method has been developed for quinoxaline synthesis from inexpensive and readily available diamines and phenacyl bromides by catalyst- and additive-free protocol.

Quinoxaline is a ubiquitous nitrogen containing fused heterocyclic motif which paved the attention of organic and medicinal chemists due to its biological properties and pharmaceutical importance.[1] Quinoxaline containing compounds have found use as potential anticancer,[2] antiviral,[3] antibiotic,[4] and anti-inflammatory agents. A few quinoxaline containing pharmacologically active molecules are shown in figure 1. For instance, quinacillin is highly effective in penicillin sensitive or penicillinase producing strains of *staphylococcus aureus*. Brimonidine is used to treat open angle glaucoma or ocular hypertension through the mechanism of reducing the synthesis of aqueous humor. Varenicline is prescribed as a medicine to treat nicotine addiction. This scaffold was also recognised in bioacids,[5] organic synthons,[6] electroluminescent materials,[7] dyes,[8] organic semiconductors,[9] cavitands,[10] dehydroannulenes[11] and ligands in coordination chemistry[12].

Quinoxaline can be synthesized by (a) condensation of 1,2-diamines with 1,2-dicarbonyl compounds[13] (b) oxidative cyclisation of α-haloketones and 1,2 diamines[14] (c) from α-hydroxy ketones[15] (d) from epoxides[16] and (e) from diols.[17] Reported methodologies for this scaffold include various catalysts/oxidants such as Bi(0),[18] $HClO_4/SiO_2$,[19] $CeCl_3.7H_2O$,[20] DABCO,[21] TMSCl,[22] $Ga(ClO_4)_3$[23] and transition metals[24] like Mn, Ru, Pd and Cu. Solid phase synthesis[25] and microwave assisted[26] synthesis for quinoxaline derivatives are also reported. Numerous methodologies are available for quinoxaline synthesis which require either expensive catalysts or hazardous additives. One such method involves manganese(IV) dioxide catalysed quinoxaline synthesis using unsubstituted diamines and α-hydroxy ketone precursors with moderate yields and limited substrate scope *via* tandem oxidative reaction. On the other hand, hazardous perchloric acid was used to synthesize this privileged scaffold through a cyclisation-oxidation process.[19] In addition to these, stoichiometric amounts of TMSCl promoted quinoxaline synthesis was achieved, in water.[22] Furthermore, copper catalysed quinoxaline synthesis was also explored using *o*-phenylenediamines and costly terminal alkynes in presence of toxic and excess amounts of DMAP as a base[27a]. $Ga(ClO_4)_3$ catalysed cycloaddition reaction was also developed for quinoxaline synthesis.[23] Later on the utility of surfactants as microreactors was explored for quinoxaline synthesis in water using 1,2-diketones by a simple condensation approach.[27b] Subsequently quinoxaline synthesis from 1,2-diketones was done using manganese ferrite ($MnFe_2O_4$) nanoparticles.[27c] Recently Lewis acid catalysed asymmetric version of fused pyrroloquinoxaline was achieved[27d]. Cerium-oxide nanoparticles have also shown their utility in quinoxaline synthesis.[27e] In majority of these methods, toxic wastes are formed with a clear and imminent danger of environmental pollution. Eco-friendly reactions have always attracted organic chemists in which the reactions are carried out in greener solvents. Thus the development of an efficient and environmentally benign methodology for the synthesis of quinoxaline derivatives remains highly desired.

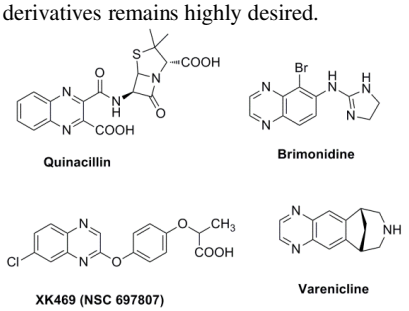

Figure 1: Biologically active scaffolds based on quinoxaline

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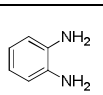
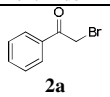
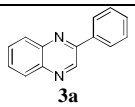
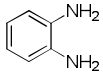
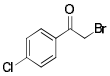
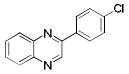
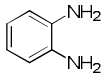
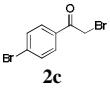
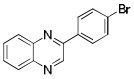
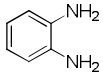
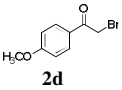
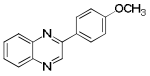
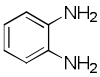
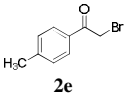
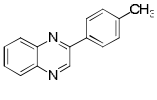
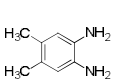
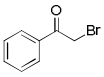
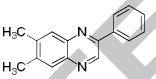
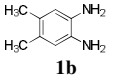
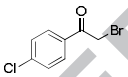
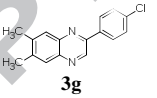
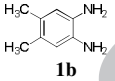
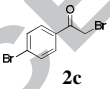
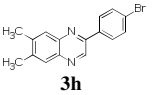
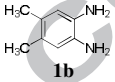
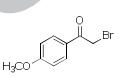
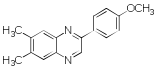
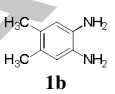
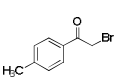
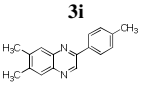
Table 1: Effect of temperature[a]

Entry	Temperature (^oC)	Time (h)	Yield[b] (%)
1	0	5	20
2	20	5	50
3	40	1	trace
4	40	2	20
5	40	3	50
6	40	4	60
7	40	5	65
8	60	5	77
9	80	2.5	85
10	80	5	87
11	100	2.5	80

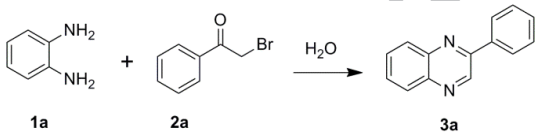
[a]Reaction condition: *o*-phenylenediamine (1.2 mmol), phenacyl bromide (1.0 mmol), water (3.0 mL). [b]Isolated yield.

Table 2: Reactions of symmetrical diamines with phenacyl bromides[a]

Entry	Diamine	Phenacyl bromide	Product	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	2.5	85
2	 **1a**	 **2b**	 **3b**	3.0	83
3	 **1a**	 **2c**	 **3c**	3.0	81
4	 **1a**	 **2d**	 **3d**	2.5	78
5	 **1a**	 **2e**	 **3e**	2.5	76
6	 **1b**	 **2a**	 **3f**	2.5	77
7	 **1b**	 **2b**	 **3g**	3.0	78
8	 **1b**	 **2c**	 **3h**	3.0	79
9	 **1b**	 **2d**	 **3i**	2.5	75
10	 **1b**	 **2e**	 **3j**	2.5	73

[a]Reaction condition: *o*-phenylenediamine (1.2 mmol), phenacyl bromide (1.0 mmol), water (3.0 mL), [b]Isolated yield.

In continuation of our work on heterocyclic chemistry,[28] we were keen to develop a catalyst free and greener approach for the synthesis of quinoxalines from 1,2-diamines and phenacyl bromides *via* a one-pot oxidative cyclization reaction in water. A typical experiment was performed by choosing *o*-phenylenediamine **1a** and phenacyl bromide **2a** as model substrates to synthesize 2-phenylquinoxaline **3a** (Scheme 1). With the advantages of using a greener solvent in mind, water was employed as the medium for the reaction. However at ambient temperature the reaction was found to be sluggish. To accelerate the reaction, dependence on temperature was examined at intervals of 20^{o}C over a range from 0 to 100^{o}C. As the temperature increased the yield of the product also increased affording a maximum yield of 85% at 80^{o}C. More noticeably the time of the reaction was reduced to 2.5h and the results obtained are summarised in Table 1.



1a **2a** **3a**

Scheme 1: One pot synthesis of quinoxaline through oxidative condensation

To generalise the scope of the reaction, experiments were performed with various symmetrical diamines and substituted phenacyl bromides containing electron withdrawing as well as electron donating groups. The results are provided in Table 2. The reaction proceeded smoothly in all the cases illustrating that the presence of withdrawing/donating substituents on the aromatic ring of phenacyl bromide was well tolerated. The reaction was further examined by employing unsymmetrical diamines which would afford the regioisomeric products. With electron withdrawing substituents on the phenylene diamines, two regioisomeric products with substituents at positions 6 and 7 were obtained in a ratio of 2:1 respectively. The isomers were separable by column chromatography using a mixture of EtOAc/Hexane. However with electron donating groups, an inseparable mixture of the regioisomers were obtained (Table 3). Based on these observations, we envisaged a plausible reaction mechanism for the formation of quinoxaline derivatives from *o*-phenylenediamine and phenacyl bromide (Figure 2). Initially a nucleophilic substitution occurs on the phenacyl bromide to afford the intermediate **3**. Intermediate **3** spontaneously cyclises to form 3-phenyl-1,2-dihydroquinoxaline **4**, which undergoes aromatization under air oxidation to afford 2-phenylquinoxaline **5** as the final product.

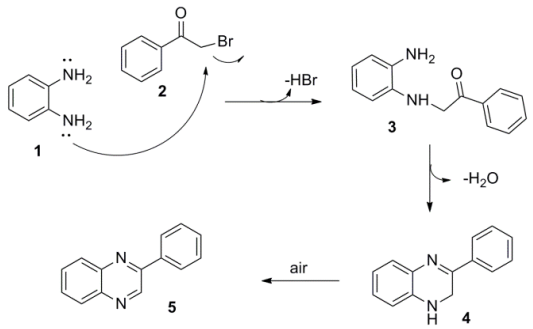
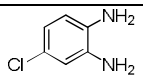
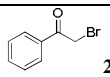
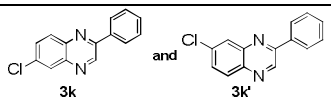
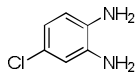
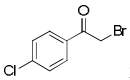
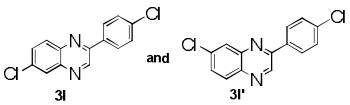
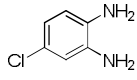
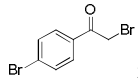
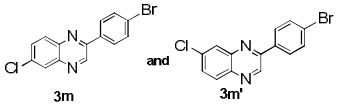
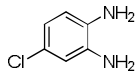
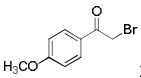
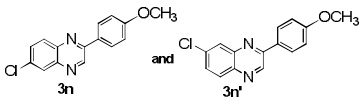
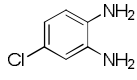
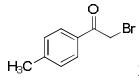
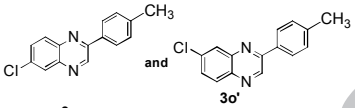
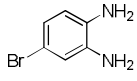
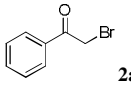
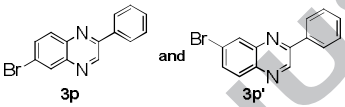
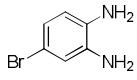
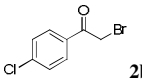
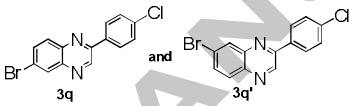
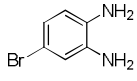
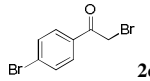
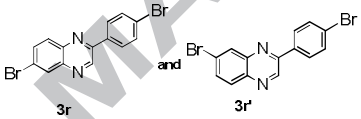
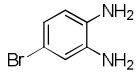
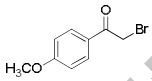
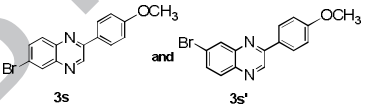
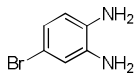
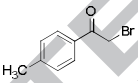
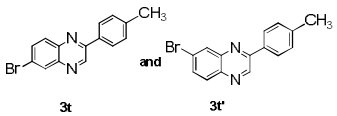
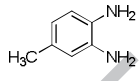
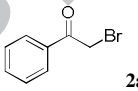
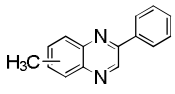
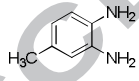
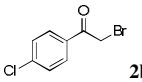
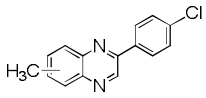
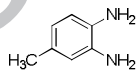
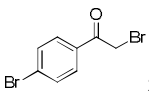
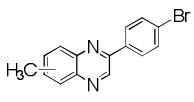
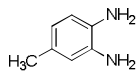


Figure 2: Plausible reaction mechanism

In conclusion, we present here a catalyst or additive free methodology for quinoxaline synthesis from substituted *o*-phenylenediamines and *α*-bromoketones. The overall procedure involves substitution, cyclisation and aromatisation reactions in a one-pot process under environmentally benign conditions.

Table 3: Reactions of unsymmetrical diamines with phenacyl bromides[a]

Entry	Diamine	Phenacyl bromide	Products	Time (h)	Yield[b](%) Ratio of isomers
1	 **1c**	 **2a**	 **3k** and **3k'**	2.5	78[b] (2:1)[c]
2	 **1c**	 **2b**	 **3l** and **3l'**	3.0	78[b] (2:1)[c]
3	 **1c**	 **2c**	 **3m** and **3m'**	3.0	81[b](2:1)[c]
4	 **1c**	 **2d**	 **3n** and **3n'**	2.5	75[b] (2:1)[c]
5	 **1c**	 **2e**	 **3o** and **3o'**	2.5	75[b](2:1)[c]
6	 **1d**	 **2a**	 **3p** and **3p'**	2.5	78[b] (2:1)[c]
7	 **1d**	 **2b**	 **3q** and **3q'**	2.5	78[b] (2:1)[c]
8	 **1d**	 **2c**	 **3r** and **3r'**	3.0	75[b] (2:1)[c]
9	 **1d**	 **2d**	 **3s** and **3s'**	2.5	75[b] (2:1)[c]
10	 **1d**	 **2e**	 **3t** and **3t'**	3.0	72[b] (2:1)[c]
11	 **1e**	 **2a**	 **3u**	2.0	78[b] (10:7)[c,d]
12	 **1e**	 **2b**	 **3v**	2.5	77[b] (10:7)[c,d]
13	 **1e**	 **2c**	 **3w**	2.5	76[b] (10:7)[c,d]
14	 **1e**	**2d**	**3x**	2.0	79[b] (10:7)[c,d]
15	**1e**	**2e**	**3y**	2.0	78[b] (10:7)[c,d]

[a]Reaction condition: Substituted *o*-phenylenediamine (1.2 mmol), phenacyl bromide (1.0 mmol), water (3.0 mL),[b]Overall isolated yield,[c]Ratio of regioisomers were determined by ^{1}H NMR from the reaction mixture, [d]Mixture of regioisomers.

Acknowledgments

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Supplementary Material

Supplementary material which includes experimental procedures, compound data and scanned spectra (^{1}H NMR, ^{13}C NMR and HRMS) can be found in the online version.

References

1. (a) Saifina, D. F.; Mamedov, V. A. *Russ. Chem. Rev*. **2010**, *79*, 351; (b) Gobec, S.; Urleb, U. *In Science of Synthesis*; 2004; Vol. 16, p 845–911 (c) Patidar, A. K.; Jeyakanda, M.; Mobiya, A. K.; Selvam, G. *Int. J. PharmTech. Res*. **2011**, *3*, 386; (d) Seitz, L. E.; Suling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2002**, *45*, 5604; (e) Weissberger, A., Taylor, E. C., Eds.; *The Chemistry of Heterocyclic Compounds*, *Wiley-Interscience*: New York, 1979.
2. (a) Jaso, A.; Zarranz, B.; Aldana, I.; Monge, A. *J. Med. Chem.* **2005**, *48*, 2019; (b) Lindsley, C. W.; Zhao, Z.; Leister, W. H.; Robinson, R. G.; Barnett, S. F.; Defeozones, D.; Jones, R. E.; Hartman, G. D.; Huff, J. R.; Huber, H. E.; Duggan, M. E. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 761.
3. Loriga, M.; Piras, S.; Sanna, P.; Paglietti, G. *Farmaco* **1997**, *52*, 157.
4. Brown, D. J., Taylor, E. C., Wipf, P., *The Chemistry of Heterocyclic Compounds-Quinoxalines: Supplements II; John Wiley and Sons*: New Jersey, 2004.
5. (a) Sarges, R.; Howard, H. R.; Browne, R. G.; Lebel, L. A.; Seymour, P. A. *J. Med. Chem*. **1990**, *33*, 2240; (b) Gazit, A.; App, H.; McMahon, G.; Chen, J.; Levitzki, A.; Bohmer, F. D. *J. Med. Chem*. **1996**, *39*, 2170.
6. Jonathan, L. S.; Hiromitsu, M.; Toshihisa, M.; Vincent, M. L.; Hiroyuki, F. *Chem. Commun*. **2002**, 862.
7. Thomas, K. R. J.; Velusamy, M.; Lin, J. T.; Chuen, C.-H.; Tao, Y.-T. *Chem. Mater*. **2005**, *17*, 1860.
8. (a) Katoh, A.; Yoshida, T.; Ohkanda, J. *Heterocycles* **2000**, *52*, 911; (b) Brock, E. D.; Lewis, D. M.; Yousaf, T. I.; Harper, H. H. U.S. Patent WO9951688, 1999.
9. (a) Dailey, S.; Feast, J. W.; Peace, R. J.; Sage, I. C.; Till, S.; Wood, E. L. *J. Mater. Chem*. **2001**, *11*, 2238.
10. (a) Jonathan, L. S.; Hiromitsu, M.; Toshihisa, M.; Vincent, M. L.; Hiroyuki, F. *J. Am. Chem. Soc.* **2002**, *124*, 13474; (b) Peter, P. C.; Gang, Z.; Grace, A. M.; Carlos, H.; Linda, M. G. T. *Org. Lett*. **2004**, *6*, 333.
11. Sascha, O.; Rudiger, F. *Synlett*. **2004**, 1509.
12. (a) Saravanakumar, S.; Kindermann, M. K.; Heinicke, J.; Kockerling, M. *Chem. Commun*. **2006**, 640; (b) Kulkarni, M. S.; Kumbhar, A. S.; Mohan, H.; Rao, B. S. M. *Dalton Trans*. **2009**, 6185.
13. (a) Darabi, H. R.; Mohandessi, S.; Aghapoor, K.; Mohsenzadeh, F. *Catal. Commun*. **2007**, *8*, 389; (b) Heravi, M. M.; Taheri, S.; Bakhtiari, K.; Oskooie, H. A. *Catal. Commun*. **2007**, *8*, 211; (c) Huang, T. K.; Wang, R.; Shi, L.; Lu, X. X. *Catal. Commun*. **2008**, *9*, 1143; (d) More, S. V.; Sastry, M. N. V.; Yao, C.-F. *Green Chem*. **2006**, *8*, 91; (e) Bhosale, R. S.; Sarda, S. R.; Andhapure, S. S.; Jadhav, W. N.; Bhusare, S. R.; Pawar, R. P. *Tetrahedron Lett*. **2005**, *46*, 7183; (f) Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett*. **2004**, *45*, 4873.
14. (a) Singh, S. K.; Gupta, P.; Duggineni, S.; Kundu, B. *Synlett* **2003**, 2147; (b) Wan, J. P.; Gan, S. F.; Wu, J. M.; Pan, Y. *Green Chem.* **2009**, *11*, 1633; (c) Ghosh, P.; Mandal, A. *Tetrahedron Lett.* **2012**, *53*, 6483;(d) Madhav, B.; Murthy, S. N.; Reddy, V. P.; Rao, K. R.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2009**, *50*, 6025.
15. (a) Raw, S. A.; Wilfred, C. D.; Taylor, R. J. K. *Org. Biomol. Chem.* **2004**, *2*, 788; (b) Kim, S. Y.; Park, K. H.; Chung, Y. K. *Chem. Commun*. **2005**, 1321; (c) Sithambaram, S.; Ding, Y.; Li, W.; Shen, X.; Gaenzler, F.; Suib, S. L. *Green Chem*. **2008**, *10*, 1029; (d) Cho, C. S.; Oh, S. G. *J. Mol. Catal. A: Chem*. **2007**, *276*, 205.
16. Antoniotti, S.; Dunach, E. *Tetrahedron Lett*. **2002**, *43*, 3971.
17. Cho, C. S.; Oh, S. G. *Tetrahedron Lett*. **2006**, *47*, 5633.
18. Yadav, J. S.; Reddy, B. V. S.; Premalatha, K.; Shankar, K. S. *Synthesis* **2008**, *23*, 3787.
19. Das, B.; Venkateswarlu, K.; Suneel, K.; Majhi, A. *Tetrahedron Lett*. **2007**, *48*, 5371.
20. Narsaiah, A. V.; Kumar, J. K. *Synth. Commun*. **2012**, *42*, 883.
21. Meshram, H. M.; Kumar, S. G.; Ramesh, P.; Reddy, B. C. *Tetrahedron Lett*. **2010**, *51*, 2580.
22. Wan, J. P.; Gan, S. F.; Wu, J. M.; Pan, Y. J. *Green Chem.* **2009**, *11*, 1633.
23. Pan, F.; Chen, T.; Cao, J.; Zou, J.; Zhang, W. *Tetrahedron Lett*. **2012**, *53*, 2508.
24. (a) Raw, S. A.; Wilfred, C. D.; Taylor, R. J. K. *Chem. Commun*. **2003**, 2286; (b) Kim, S. Y.; Park, K. H.; Chung, Y. K. *Chem. Commun*. **2005**, 1321; (c) Robinson, R. S.; Taylor, R. J. K. *Synlett* **2005**, 1003; (d) Marques, C. S.; Moura, N.; Burke, A. J. *Tetrahedron Lett*. **2006**, *47*, 6049; (e) Cho, C. S.; Oh, S. G. *J. Mol. Catal. A: Chem.* **2007**, *276*, 205; (f) Akkilagunta, V. K.; Reddy, V. P.; Kakulapati, R. R. *Synlett* **2010**, 2571.
25. Liu, J.; Liu, J.; Wang, J.; Jiao, D.; Liu, H. *Synth. Commun*. **2010**, *40*, 2047.
26. Zhou, J.; Gong, G.; Zhi, S.; Duan, X. *Synth. Commun*. **2009**, *39*, 3743.
27. (a) Wang, W.; Shen, Y.; Meng, X.; Zhao, M.; Chen, Y.; Chen, B. *Org. Lett.* **2011**, *13*, 4514; (b) Kumar, D.; Seth, K.; Kommi, D. N.; Bhagat, S. Chakraborti, A. K. *RSC Adv*. **2013**, *3*, 15157; (c) Brahmachari, G.; Laskar S.; Barik, P. *RSC Adv*. **2013**, 3, 14245; (d) Li, Y.; Su, Y-H.; Dong, D-J.; Wu, Z.; Tian, S-K. *RSC Adv*. **2013**, *3*, 18275; (e) Edayadulla, N.; Lee, Y. R. *RSC Adv*. **2014**, *4*, 11459.
28. (a) Kumar, V.; Nair, V. A. *Tetrahedron Lett*. **2010**, *51*, 966; (b) Khatik, G. L.; Pal, A.; Mobin, S. M.; Nair, V. A. *Tetrahedron Lett*. **2010**, *51*, 3654; (c) Khatik, G. L.; Kaur, J.; Kumar, V.; Tikoo, K.; Venugopalan , P.; Nair, V. A. *Eur. J. Med. Chem.* **2011**, *46*, 3291; (d) Kumar, V.; Raghavaiah, P.; Mobin, S. M.; Nair, V. A. *Org. Biomol. Chem.* **2010**, *8*, 4960; (e) Kumar, V.; Pal, A.; Khatik, G. L.; Nair, V. A. *Tetrahedron: Asymmetry* **2012**, *23*, 434; (f) Kumar, V.; Kumar, K.; Pal, A.; Khatik G. L.; Nair, V. A. *Tetrahedron* **2013**, *69*, 1747; (g) Khatik, G. L.; Kumar, V.; Nair, V. A. *Org. Lett*. **2012**, *14*, 2442; (h) Chouhan, M.; Sharma, R.; Nair, V. A. *Org. Lett*. **2012**, *14*, 5672; (i) Chouhan, M.; Senwar, K. R.; Sharma, R.; Grover, V.; Nair, V. A. *Green Chem*. **2011**, *13*, 2553; (j) Goyal, S.; Patel, J. K.; Gangar, M.; Kumar, K.; Nair, V. A. *RSC Adv*. **2015**, 5, 3187.