Monatsh Chem (2010) 141:317–322
DOI 10.1007/s00706-010-0252-1

ORIGINAL PAPER

# ZnO-nanoparticle-promoted synthesis of polyhydroquinoline derivatives via multicomponent Hantzsch reaction

**M. Z. Kassaee · Hassan Masrouri · Farnaz Movahedi**

Received: 9 July 2009 / Accepted: 7 January 2010 / Published online: 17 March 2010


**Abstract** Zinc oxide nanoparticles are used as an effective and reusable catalyst for one-pot, four-component couplings of aldehydes, dimedone, active methylene compounds, and ammonium acetate to produce polyhydroquinoline derivatives under solvent-free conditions at room temperature. Compared with other methods, satisfactory results are obtained with high yields, short reaction times, and simplicity in the experimental procedure. The catalyst could easily be recycled and reused four times without noticeable decrease in catalytic activity.

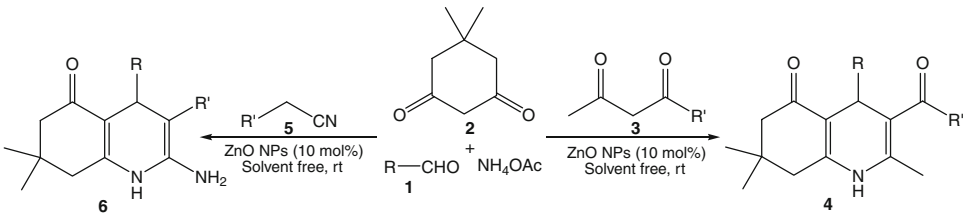
**Keywords** ZnO nanoparticles · Polyhydroquinoline derivatives · Heterogeneous catalyst · Hantzsch reaction · Solvent-free

## Introduction

Nanotechnology is of growing importance in many branches of research because of the opportunity for miniaturization and the interesting properties associated with small particle size [1]. In recent decades, nanostructured materials have attracted much attention for their novel electronic, magnetic, optical, chemical, and mechanical properties due to their unique characteristics which are different from bulk materials [2–4]. One of the interesting studies in this area is that of transition-metal oxide nanoparticles. Specifically, zinc oxide nanoparticles (ZnO NPs) have great potential for use as a catalyst for a variety of organic and inorganic reactions due to their high surface-to-volume ratio [5]. Also, since ZnO NPs are often recovered easily by simple workups, which prevents contamination of products, they may be considered as a promising safe and reusable catalyst. Hence, the inexpensive and highly efficient ZnO NPs are used in the synthesis of $\beta$-phosphono malonates [6], Knoevenagel condensation [7], Dakin–West reaction [8], degradation of acid red B and rhodamine B [9], etc.

On the other hand, 1,4-dihydropyridines (1,4-DHPs), as important "privileged scaffolds," are very attractive targets for medicinal synthesis. A recent literature survey revealed that 1,4-DHPs have several biological applications, including vasodilator, bronchodilator, geroprotective, hepatoprotective, neuroprotective [10], chemosensitizer behavior in tumor therapy [11], as well as cerebral antiischemic activity in the treatment of Alzheimer's disease. They can cure the disordered heart rate as a chain-cutting agent of factor IV channel and also possess calcium channel agonist–antagonist modulation activities [12–16]. Cardiovascular agents such as nifedipine, nicardipine, amlodipine, and other related derivatives are dihydropyridyl compounds, which are effective for the treatment of hypertension [17–19]. As valuable drug candidates, polyhydroquinolines not only have attracted the attention of chemists for synthesis but also represent an interesting research challenge. Experimentally, the preparation of the 1,4-DHPs was first reported by Hantzsch through a multicomponent, one-step cyclocondensation reaction. Due to the modest yield of this method, numerous improvements have since been developed, including the use of microwaves [20–22], ionic liquids [23, 24], grinding [25], refluxing at high temperature [26–29], $Bu_4NHSO_4$ [30], L-proline [31], HY-zeolite [32], silica-supported acids [33, 34], boronic acids [35, 36], TMSCl–NaI [37], ceric ammonium nitrate (CAN) [38, 39], metal triflates [40, 41],

M. Z. Kassaee (✉) · H. Masrouri · F. Movahedi
Department of Chemistry, Tarbiat Modares University, P.O. Box 14155-4838, Tehran, Iran
e-mail: kassaeem@modares.ac.ir




**Scheme 1**

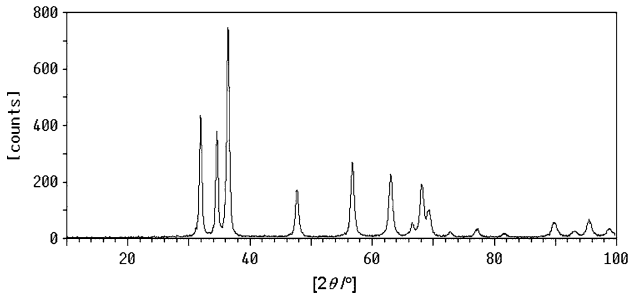



**Fig. 1** X-ray diffraction pattern of the synthesized ZnO NPs

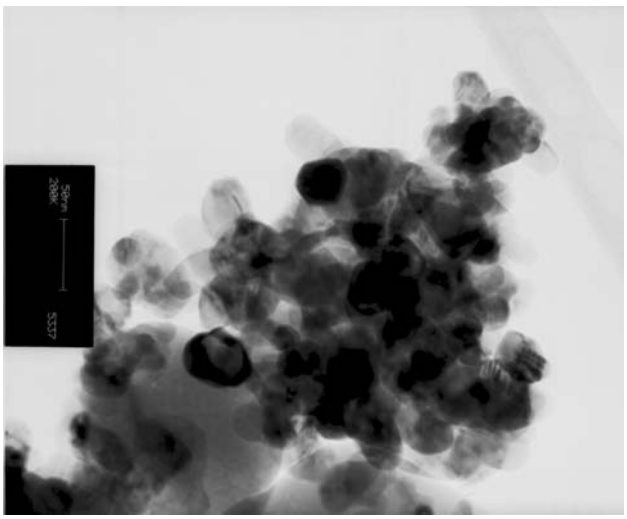


**Fig. 2** TEM image of the synthesized ZnO NPs

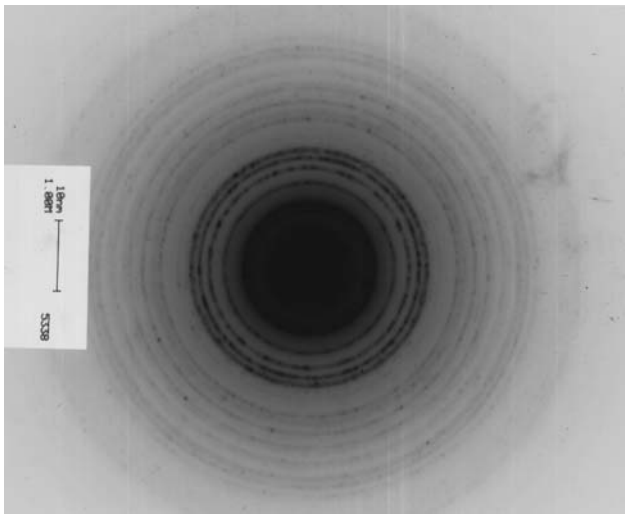


**Fig. 3** Selected-area electron diffraction (SAED) pattern of ZnO NPs

baker's yeast [42, 43], and *p*-TSA [44]. Nevertheless, many of these methods still suffer from several drawbacks, such as unsatisfactory yield, use of ecologically suspected organic solvents, high temperature, long reaction time, as well as the use of expensive and nonreusable catalysts. Therefore, investigation for improved reaction conditions for synthesis of polyhydroquinoline derivatives using efficient and reusable catalysts under solvent-free conditions is of prime importance.

In this report we employ ZnO NPs as an efficient and heterogeneous catalyst for synthesis of polyhydroquinoline derivatives through one-pot, four-component reactions of aldehydes, dimedone, active methylene compounds, and ammonium acetate under solvent-free conditions at room temperature (Scheme 1).

## Results and discussion

We first prepared ZnO NPs through a solid-state reaction method reported by Zhu and co-workers [45]. The X-ray diffraction (XRD) patterns of the ZnO NPs (Fig. 1) could be indexed to the hexagonal wurtzite structure (space group: $P63mc$; $a = 3.249$ Å, $c = 5.206$ Å, JCPDS card no. 36-1451). No impurities were involved in the synthesized ZnO NPs sample, for which an average size of 21 nm was estimated by Scherrer's equation, $D_{h,k,l} = k\lambda/\beta \cos\theta$, where $k$ is a constant (generally considered as 0.89 for ZnO), $\lambda$ is the wavelength of Cu $K_\alpha$ (1.54 Å), $\beta$ is the corrected diffraction line full-width at half-maximum (FWHM), and $\theta$ is Bragg's angle [46] .

The morphology and grain size of the ZnO NPs were investigated by Transmission electron microscopy (TEM) (Fig. 2). They had spherical and hexagonal morphology with a narrow size distribution from 18 to 36 nm and a mean grain size of 21 nm, confirming the results calculated from Scherrer's equation. The presence of some larger particles should be attributed to aggregating or overlapping of smaller particles. The selected-area electron diffraction

**Table 1** Zinc oxide nanoparticles (ZnO NPs)-catalyzed four-component synthesis of polyhydroquinoline derivatives

| Entry | R | R′ | Product | Time (min) | Yield (%)[a] | M.p. (°C) | M.p. (°C) [Ref.] |
|---|---|---|---|---|---|---|---|
| 1 | Ph | OEt | **4a** | 20 | 98 | 202–203 | 202–204 [40] |
| 2 | Ph | OMe | **4b** | 20 | 96 | 212–214 | 213–215 [25] |
| 3 | 4-MeO–$C_6H_4$ | OEt | **4c** | 15 | 96 | 254–256 | 257–259 [40] |
| 4 | 4-MeO–$C_6H_4$ | OMe | **4d** | 15 | 92 | 251–252 | 248–250 [25] |
| 5 | 4-Me–$C_6H_4$ | OEt | **4e** | 25 | 95 | 261–263 | 260–261 [40] |
| 6 | 4-Me–$C_6H_4$ | OMe | **4f** | 25 | 95 | 270–274 | 283–285 [25] |
| 7 | 4-Cl–$C_6H_4$ | OEt | **4g** | 20 | 98 | 245–246 | 244–246 [39] |
| 8 | 4-Cl–$C_6H_4$ | OMe | **4h** | 20 | 96 | 220–223 | 221–222 [25] |
| 9 | 3-Cl–$C_6H_4$ | OEt | **4i** | 30 | 92 | 231–233 | 234–235 [38] |
| 10 | 2-Cl–$C_6H_4$ | OEt | **4j** | 30 | 91 | 208–210 | 209–211 [25] |
| 11 | 2,4-$Cl_2$–$C_6H_3$ | OEt | **4k** | 25 | 93 | 240–242 | 241–244 [40] |
| 12 | 3,4-$Cl_2$–$C_6H_3$ | OEt | **4l** | 20 | 92 | 214–215 | 214–216 [39] |
| 13 | 4-Br–$C_6H_4$ | OEt | **4m** | 20 | 97 | 252–253 | 253–255 [40] |
| 14 | 4-F–$C_6H_4$ | OEt | **4n** | 30 | 91 | 184–185 | 184–186 [40] |
| 15 | 4-$NO_2$–$C_6H_4$ | OEt | **4o** | 15 | 89 | 241–242 | 245–246 [25] |
| 16 | 3-$NO_2$–$C_6H_4$ | OEt | **4p** | 20 | 90 | 177–178 | 176–179 [31] |
| 17 | 2-$NO_2$–$C_6H_4$ | OEt | **4q** | 20 | 89 | 210–212 | 208–211 [31] |
| 18 | 4-OH–$C_6H_4$ | OEt | **4r** | 20 | 86 | 232–234 | 232–234 [40] |
| 19 | 4-OH, 3-OMe–$C_6H_3$ | OEt | **4s** | 15 | 89 | 206–208 | 211–212 [39] |
| 20 | $C_6H_5$–CH=CH | OEt | **4t** | 25 | 91 | 204–206 | 204–206 [39] |
| 21 | 4-$Me_2N$–$C_6H_4$ | OEt | **4v** | 30 | 85 | 230–232 | 229–231 [40] |
| 22 | 2-Thienyl | OEt | **4w** | 20 | 87 | 240–242 | 241–244 [25] |
| 23 | 2-Furyl | OEt | **4x** | 20 | 91 | 246–247 | 246–248 [40] |
| 24 | 3-Pyridyl | OEt | **4y** | 25 | 91 | 66–67 | 66–67 [40] |
| 25 | $C_2H_5$ | OEt | **4z** | 40 | 84 | 145–146 | 145–146 [40] |
| 26 | *n*-$C_3H_7$ | OEt | **4aa** | 40 | 87 | 145–147 | 144–146 [25] |
| 27 | Ph | CN | **6a** | 20 | 91 | 272–273 | 275–277 [25] |
| 28 | Ph | $CO_2Et$ | **6b** | 30 | 88 | 148–151 | 150–155 [25] |
| 29 | 4-MeO–$C_6H_4$ | CN | **6c** | 15 | 93 | 287–289 | 289–293 [25] |
| 30 | 4-MeO–$C_6H_4$ | $CO_2Et$ | **6d** | 25 | 85 | 125–127 | 122–125 [25] |
| 31 | 4-Cl–$C_6H_4$ | CN | **6e** | 15 | 95 | 285–286 | 287–288 [25] |
| 32 | 4-Cl–$C_6H_4$ | $CO_2Et$ | **6f** | 25 | 91 | 173–175 | 174–176 [25] |
| 33 | 4-Me–$C_6H_4$ | CN | **6g** | 20 | 89 | 286–288 | 294–295 [25] |
| 34 | 4-Me–$C_6H_4$ | $CO_2Et$ | **6h** | 30 | 83 | 133–134 | 135–137 [25] |

Reaction conditions: benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), dimedone (2 mmol), ammonium acetate (2 mmol), and catalyst (10 mol%) at room temperature under solvent-free conditions

[a] Isolated yields

(SAED) pattern of ZnO NPs clearly shows the crystalline nature of the product, indexed to (100) (002), (101), (102), (110), and (103), respectively, for the diffraction rings, in accordance with similar peaks in the XRD pattern (Fig. 3).

The prepared ZnO NPs were investigated as a catalyst in the synthesis of polyhydroquinoline derivatives. For this purpose, cyclocondensation of benzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate was examined in the presence of a catalytic amount of ZnO NPs (10 mol%) under solvent-free conditions at room temperature, which afforded ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenylquinoline-3-carboxylate in 98% yield. In order to observe the versatility of the procedure, active methylene compounds including methyl acetoacetate and ethyl acetoacetate ($\beta$-ketoesters), malononitrile, as well as ethyl cyanoacetate were taken in the same experiment. Also, it was found that the reaction can tolerate a wide range of aliphatic, heterocyclic, and aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents in the *ortho*, *meta*, and *para* positions (Table 1). All products were characterized on the basis of their spectroscopic data such as infrared (IR) and

$^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR), as well as physical data.

In comparison with the same reaction catalyzed by commercially available bulk ZnO [47], use of ZnO NPs reduced the reaction time by a factor of six, with higher yields (Table 2, entries 11 and 14). To investigate the effects of media, we carried out the condensation of benzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate in various organic solvents at room temperature using 10 mol% ZnO NPs as the catalyst. Obviously, the polar solvents such as ethanol and acetonitrile (Table 2, entries 1 and 2) were much better than nonpolar solvents (Table 2, entries 6 and 7). This could be attributed to different solubility of ammonium acetate in the solvents. Ultimately, solvent-free conditions were preferred due to high yields and short reaction times.

In evaluating the effects of catalyst concentration, the best yields were found in the presence of just 10 mol% ZnO NPs. A higher amount of catalyst (20 mol%) did not improve the results to an appreciable extent (Table 2, entry 15). We also carried out the model reaction without any catalyst, but the product was isolated in poor yield (21%), while the major product obtained was a dimedone aldehyde adduct. Therefore, the catalyst plays a crucial role in the success of the reaction in terms of rate and yields of polyhydroquinoline derivatives.

The catalytic activity and the ability to recycle and reuse ZnO NPs were studied in this system (Table 3). The catalyst was separated by centrifuging the aqueous layer at 3,000 rpm at 20 °C for 3 min, and was reused as such for subsequent experiments under similar reaction conditions. The yields of **4a** decreased only slightly with reuse of ZnO NPs four times.

A conceivable mechanism for the formation of the product would be as follows. The ZnO NPs facilitate the Knoevenagel-type coupling as well as enaminone formation through Lewis acid sites ($Zn^{2+}$) coordinated to the oxygen of carbonyl groups. On the other hand, ZnO NPs can activate methylene compounds so that deprotonation of the C–H bond occurs in the presence of Lewis basic sites ($O^{2-}$). As a result the formation of polyhydroquinoline derivatives proceeds by activation of reactants through both Lewis acid and basic sites of ZnO NPs.

A comparison of the efficiency of catalytic activity of the ZnO NPs with several previous methods is presented in Table 4. The results show that this method is superior to some of the earlier methods in terms of yield and reaction time.

## Conclusion

The present four-component, one-pot condensation for synthesis of polyhydroquinolines by ZnO nanoparticles

**Table 2** Optimization of the ZnO-NPs-catalyzed model reaction for synthesis of polyhydroquinoline derivatives

| Entry | Solvent | Catalyst | Time (min) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | MeCN | ZnO NPs (10%) | 180 | 73 |
| 2 | EtOH | ZnO NPs (10%) | 60 | 84 |
| 3 | THF | ZnO NPs (10%) | 120 | 62 |
| 4 | $H_2O$ | ZnO NPs (10%) | 90 | 71 |
| 5 | Acetone | ZnO NPs (10%) | 240 | 60 |
| 6 | Toluene | ZnO NPs (10%) | 720 | 37 |
| 7 | $CH_2Cl_2$ | ZnO NPs (10%) | 720 | 46 |
| 8 | Neat | No catalyst | 180 | 21 |
| 9 | Neat | No catalyst | 120 | 53[b] |
| 10 | Neat | Bulk ZnO (5%) | 120 | 55 |
| 11 | Neat | Bulk ZnO (10%) | 120 | 71 |
| 12 | Neat | Bulk ZnO (20%) | 120 | 72 |
| 13 | Neat | ZnO NPs (5%) | 90 | 83 |
| 14 | Neat | ZnO NPs (10%) | 20 | 98 |
| 15 | Neat | ZnO NPs (20%) | 20 | 98 |

Reaction conditions: benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), dimedone (2 mmol), ammonium acetate (2 mmol), and catalyst

[a] Isolated yields

[b] Reaction carried out at 60 °C

**Table 3** Reusability of the ZnO NPs catalyst

| Run | Yield (%) | Recovery of ZnO NPs (%) |
|---|---|---|
| 1 | 98 | 99 |
| 2 | 97 | 99 |
| 3 | 97 | 98 |
| 4 | 95 | 96 |

Reaction conditions: benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), dimedone (2 mmol), ammonium acetate (2 mmol), and catalyst at room temperature under solvent-free conditions

**Table 4** Comparison of catalytic activity of ZnO NPs with several known catalysts

| Entry | Conditions | Yields (%) | Ref. |
|---|---|---|---|
| 1 | CAN, EtOH, rt, 1 h | 92 | [38] |
| 2 | L-Proline, solvent free, rt, 0.5 h | 95 | [31] |
| 3 | $Yb(OTf)_3$, EtOH, rt, 5 h | 90 | [40] |
| 4 | $Sc(OTf)_3$, EtOH, rt, 4 h | 93 | [41] |
| 5 | HY-Zeolite, $CH_3CN$, rt, 2 h | 93 | [32] |
| 6 | Baker's yeast, rt, 24 h | 79 | [43] |
| 7 | *p*-TSA, EtOH, rt, 2 h | 93 | [44] |
| 8 | ZnO NPs, Solvent free, rt, 20 min | 98 | This work |

Reaction conditions: benzaldehyde, ethyl acetoacetate, dimedone, ammonium acetate, and catalyst

catalysis provides an efficient, facile, and environmentally acceptable modification of Hantzsch synthesis. This method offers several advantages including high yield, short reaction time, a simple work-up procedure with solvent-free conditions, ease of separation and recyclability of the catalyst, as well as the ability to tolerate a wide variety of substitutions in the components.

## Experimental

### *General methods*

Nanostructures were characterized using a Holland Philips Xpert X-ray powder diffraction (XRD) diffractometer (Cu $K_\alpha$ radiation, $\lambda = 0.154056$ nm), at scanning speed of 2°/min from 10° to 100° ($2\theta$). Particle size and morphology were investigated by a JEOL JEM-2010 transmission electron microscope (TEM) with accelerating voltage of 200 kV. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-460 spectrometer. $^1$H and $^{13}$C spectra were measured at 500.1 and 125.7 MHz, respectively, on a Bruker DRX 500 Avance FT-NMR instrument with DMSO-$d_6$ as solvent. Reagents and solvents were obtained from Fluka (Buchs, Switzerland) and used without further purification.

### *General procedure for synthesis of ZnO nanoparticles*

In a solid-state reaction condition, 2.19 g $Zn(CH_3COO)_2 \cdot 2H_2O$ (0.01 mol) was ground for 5 min and then mixed with 1.60 g NaOH (0.04 mol). After the mixture was ground for 30 min, the product was washed three times with deionized water and ethanol to remove the by-products. The final product was first dried at 80 °C for 1 h and then calcined in air at 600 °C for 2 h to decompose $Zn(OH)_2$ into ZnO and $H_2O$.

### *General procedure for synthesis of polyhydroquinoline derivatives*

To a stirred mixture of an aldehyde (2 mmol), dimedone (2 mmol), an active methylene compound (2 mmol), and ammonium acetate (2 mmol) was added a catalytic amount of ZnO NPs (10 mol%) under solvent-free conditions at room temperature. The reaction mixture solidified within a short time. After completion, the resultant material was washed with brine and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure to yield the crude product, which was then purified by recrystallization from hot ethanol to afford polyhydroquinoline derivatives in high yield. The selected spectral data are omitted.

## References


1. Rautio J, Perämäki P, Honkamo J, Jantunen H (2009) Microchem J 91:272
2. Xia YN, Yang PD, Sun YG, Wu YY, Mayers B, Gates B, Yin YD, Kin F, Yan HQ (2003) Adv Mater 15:353
3. Wang ZL, Kong XY, Ding Y, Gao PX, Hughes WL, Yang R, Zhang Y (2004) Adv Funct Mater 14:943
4. Chae WS, Shin HW, Lee ES, Shin EJ, Jung JS, Kim YR (2005) J Phys Chem B 109:6204
5. Narayanan R, El-Sayed MA (2005) J Phys Chem B 109:12663
6. Hosseini-Sarvari M, Etemad S (2008) Tetrahedron 64:5519
7. Hosseini-Sarvari M, Sharghi H, Etemad S (2008) Helv Chim Acta 91:715
8. Mirjafary Z, Saeidian H, Sadeghi A, Matloubi Moghaddam F (2008) Catal Commun 9:299
9. Wang J, Jiang Z, Zhang Z, Xie Y, Wang X, Xing Z, Xu R, Zhang X (2008) Ultrason Sonochem 15:768
10. Klusa V (1995) Drugs Future 20:135
11. Boer R, Gekeler V (1995) Drugs Future 20:499
12. Godfraid T, Miller R, Wibo M (1986) Pharmacol Rev 38:321
13. Mager PP, Coburn RA, Solo AJ, Triggle DJ, Rothe H (1992) Drug Des Discov 8:273
14. Mannhold R, Jablonka B, Voigdt W, Schoenafinger K, Schravan K (1992) Eur J Med Chem 27:229
15. Shan R, Velazquez C, Knaus EE (2004) J Med Chem 47:254
16. Sawada Y, Kayakiri H, Abe Y, Mizutani T, Inamura N, Asano M, Hatori C, Aramori I, Oku T, Tanaka H (2004) J Med Chem 47:2853
17. Buhler FR, Kiowski W (1987) J Hypertens 5:S3
18. Bretzel RG, Bollen CC, Maeser E, Federlin KF (1993) Am J Kidney Dis 21:53
19. Reid JL, Meredith PA, Pasanisi F (1985) J Cardiovasc Pharmacol 7:S18
20. Khadikar BM, Gaikar VG, Chitnavis AA (1995) Tetrahedron Lett 36:8083
21. Öhberg L, Westman J (2001) Synlett 1296
22. Agarwal A, Chauhan PMS (2005) Tetrahedron Lett 46:1345
23. Ji SJ, Jiang ZQ, Lu J, Loh TP (2004) Synlett 831
24. Sridhar R, Perumal PT (2005) Tetrahedron 61:2465
25. Kumar S, Sharma P, Kapoor KK, Hundal MS (2008) Tetrahedron 64:536
26. Phillips AP (1949) J Am Chem Soc 71:4003
27. Anderson G Jr, Berkelhammer G (1958) J Am Chem Soc 80:992
28. Dolly HS, Chimni SS, Kumar S (1995) Tetrahedron 51:12775
29. Gordeev MF, Patel DV, Gordon EM (1996) J Org Chem 61:924
30. Tewari N, Dwivedi N, Tripathi RP (2004) Tetrahedron Lett 45:9011
31. Karade NN, Budhewar VH, Shinde SV, Jadhav WN (2007) Lett Org Chem 4:16
32. Das B, Ravikanth B, Ramu R, Rao BV (2006) Chem Pharm Bull 54:1044
33. Maheswara M, Siddaiah V, Rao YK, Tzeng Y, Sridhar C (2006) J Mol Catal A Chem 260:179
34. Gupta R, Gupta R, Paul S, Loupy (2007) Synthesis 2835
35. Sridhar R, Perumal PT (2005) Tetrahedron 61:2465
36. Debache A, Boulcina R, Belfaitah A, Rhouati S, Carboni B (2008) Synlett 509
37. Sabitha G, Reddy GSKK, ChS Reddy, Yadav JS (2003) Tetrahedron Lett 44:4129
38. Ko S, Yao CF (2006) Tetrahedron 62:7293
39. Reddy CS, Raghu M (2008) Chin Chem Lett 19:775
40. Wang LM, Sheng J, Zhang L, Han JW, Fan Z, Tian H, Qian CT (2005) Tetrahedron 61:1539
41. Donelson JL, Gibbs RA, De SK (2006) J Mol Catal A Chem 256:309

42. Lee JH (2005) Tetrahedron Lett 46:7329
43. Kumar A, Maurya RA (2007) Tetrahedron Lett 48:3887
44. Cherkupally SR (2008) Chem Pharm Bull 56:1002
45. Zhu Y, Zhou Y (2008) Appl Phys A 92:275
46. Cullity BD, Stock SR (2001) Elements of X-ray diffraction, 3rd edn. Prentice-Hall, Englewood Cliffs
47. Matloubi Moghaddam F, Saeidian H, Mirjafary Z, Sadeghi A (2009) J Iran Chem Soc 6:317